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THE

REPORT

OF THE

DEPARTMENT OF PATHOLOGY

OF

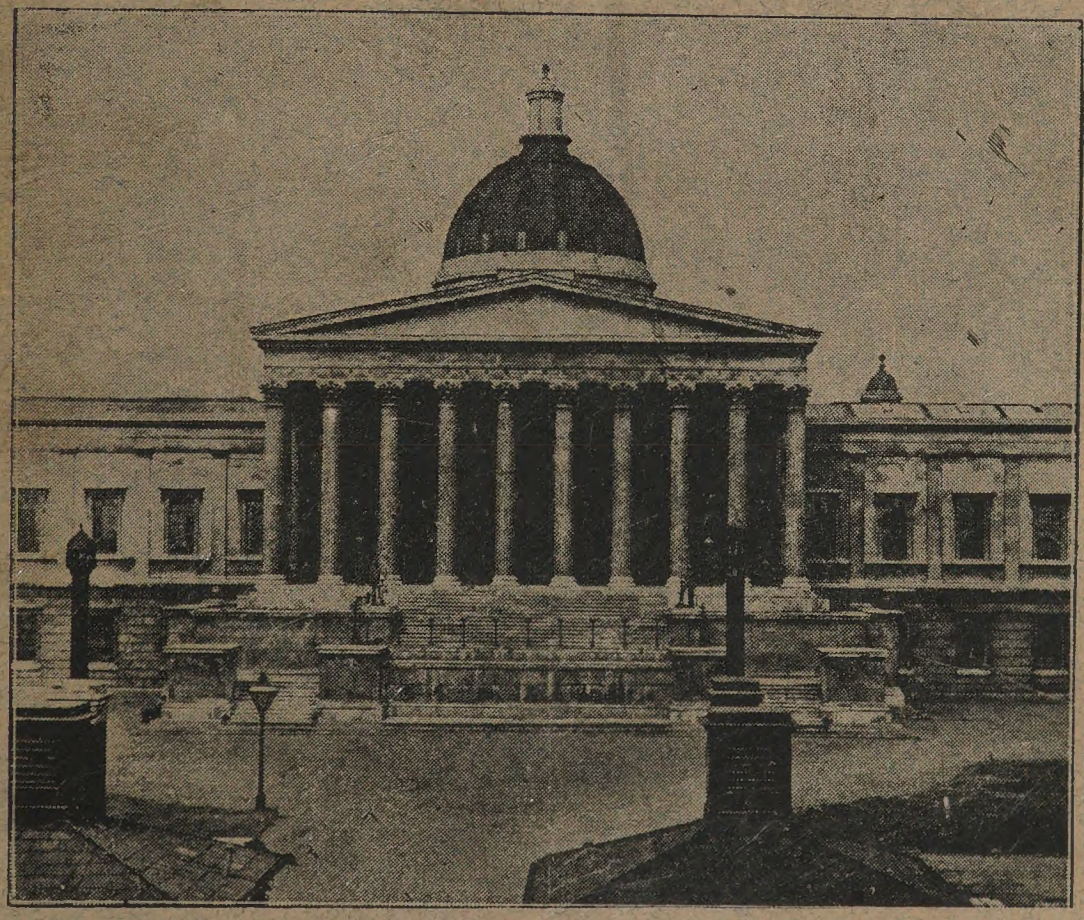
UNIVERSITY COLLEGE, LONDON.

1892-1893.

TOGETHER WITH A

COLLECTION OF PAPERS AND ABSTRACTS PUBLISHED FROM THE LABORATORY.

VOL. I.



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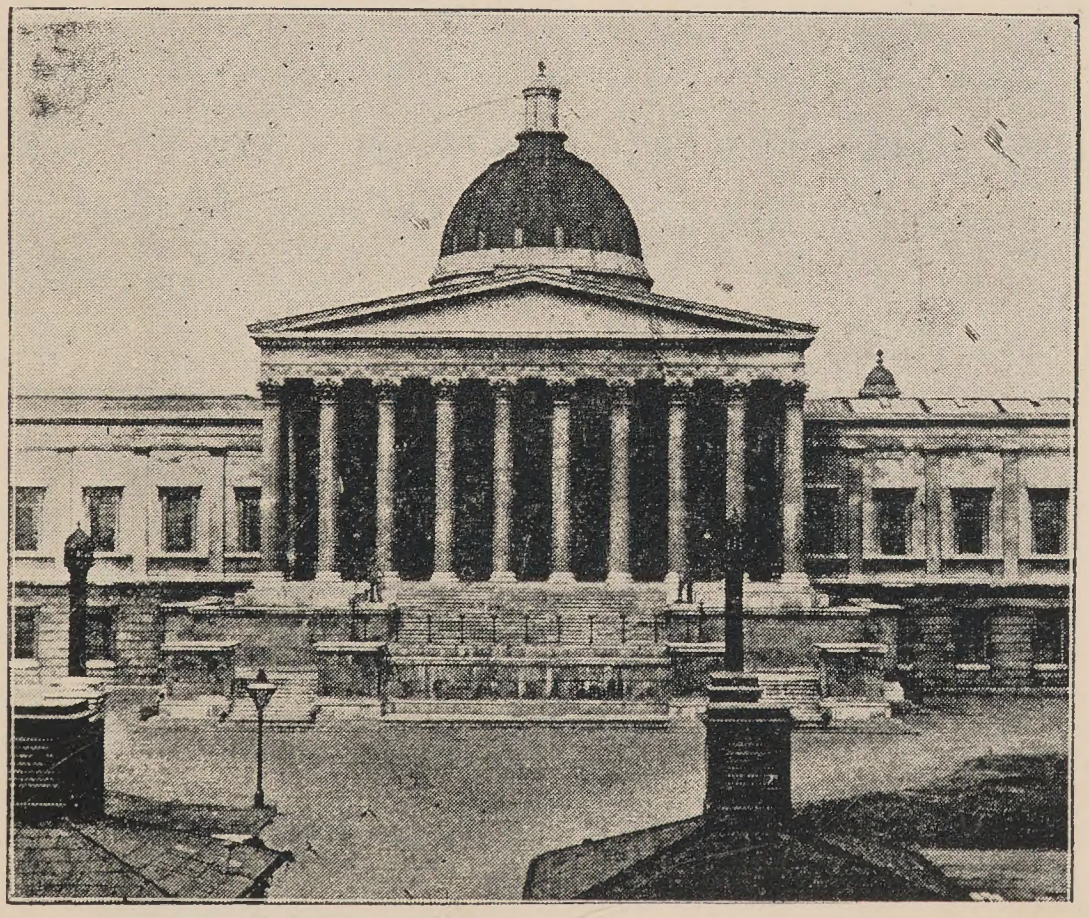

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INTRODUCTION.

This volume is the first of a series of collected papers which it is hoped may appear from year to year. The present collection includes the publications from the commencement of 1892 to May, 1893,* and represents part of the work which is being carried out in the Laboratory of Pathology. We conclude with a brief report upon the present condition of the Laboratory accommodation, and with a list of the researches finished or in progress since 1892.

*Owing to the difficulty of binding, the papers in the Philosophical transactions do not appear in this collection. They include—

The minute analysis of the facial region of the so-called facial region of the Macacus rhesus, by VICTOR HORSLEY, F.R.S., F.R.C.S., and CHARLES BEEVOR, M.D., M.R.C.P.

The nerve roots which enter into the formation of the brachial plexus, etc., of the dog, by RISIEN RUSSELL, M.B., M.R.C.P.

[*The Frontispiece is from a photograph kindly taken by R. W. Lake, M.R.C.S.*]

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PAPERS.

1.—The abductor and adductor fibres of the Recurrent Laryngeal nerve. By **J. S. Risien Russell, M.B., M.R.C.P.** (From Proc. Roy. Soc., Vol. 51, 1892).

2.—The Bacteriology of epidemic exfoliative dermatitis. By **J. S. Risien Russell, M.B., M.R.C.P.** (From Brit. Jour. Dermat. No. 42, Vol. 4, 1892).

3.—The nerve roots which enter into the formation of the Brachial plexus, etc., of the dog. By **Risien Russell, M.B., M R.C.P.** (Abstract in Proc. Roy. Soc., Vol. 51, 1892, and Phil. Trs., 1892).

4.—On the factors which produce septic peritonitis. By **Max Walthard, M.D., M.R.C.S.** Eng. of Bern. (From Brit. Med. Jour., 1892).

5.—On a new micro-organism of spreading œdema. By **A. Butler Harris, M.A., M.B., B.S.**, Oxon. (From Journal of Pathology and Bact. 1893).

6.—Madura foot of India. By **Nusserwanji Surveyor, M.D., M.R.C.P.**, of Bombay. (From Brit. Med. Jour. 1892).

7.—Enlargement of the hypophysis cerebri in myxœdema. By **Rubert Boyce** and **Cecil Beadles, M.R.C.S.** (From Jour. of Path. and Bact. 1892).

8.—A further contribution to the study of the pathology of the Hypophysis cerebri. By **Rubert Boyce, M.B.** and **Cecil Beadles, M.R.C.S.** (From Jour. of Path. and Bact. 1893).

9.—Remarks upon a case of Aspergillar pneumonomycosis. By **Rubert Boyce, M.B.** (From Jour. of Path. and Bact, 1892.

10.—Upon the action of gravity upon Bacterium Zopfii. By **Rubert Boyce, M.B.** and **Ernest Evans, M.B.** (Abstract from Proc. Roy. Soc., Vol. 53, 1893).

11.—Madura Disease. By **Rubert Boyce, M.B.** and **N. F. Surveyor, M.D.** (Abstract from Proc. Roy. Soc., 1893, and Lancet, 1893.

12.—Morphology of Tumors. By **Rubert Boyce, M.B.** (From Brit. Med. Jour. 1892). and Sporozoa and Cancer. By **Arthur Giles, M.D.** and **R. Boyce.** (From Lancet, 1893).

13.—A preliminary Report on œdema. By **Victor Horsley, B.S., F.R.C.S., F.R.S.** and **Rubert Boyce, M.B.** (From Brit. Med. Jour. 1893).

14.—Remarks on the Function of the Thyroid Gland. A critical and historical Review. By **Victor Horsley, F.R.C.S., F.R.S.** (From Brit. Med. Jour., 1892).

LABORATORY REPORT.

In 1891 a considerable portion of the Birkbeck Laboratory of Chemistry was re-modelled to meet for a time the increasing requirements of the Department of Pathology. By this means five new rooms were acquired, and the accommodation is at present arranged as follows :—

1.—**Class Room.** This room is used both for lectures and demonstrations upon the various branches of Pathology ; for research and practical work generally. It is furnished with benches, water and gas for practical work: also with a projection apparatus. It contains a collection of diseased tissues, both in macroscopical and microscopical preparations, for histological study, as well as a large collection of original paintings and drawings by Sir Robert Carswell and others illustrating diseased conditions.

2.—**Research Rooms.** The Research Room behind the Anatomy Theatre is chiefly used for experiments on the circulation and vaso-motor system. It is fitted with a Hürthle's Kymographion. In 1893 a Bunsen exhaust pump was added to this room for the separation of filtrates.

The chief Research Room, i.e. in the Birkbeck Laboratory is arranged for all kinds of research. It is fitted with a galvanometer and pillar. It also contains the nucleus of a small reference library.

3.—**Bacteriological Rooms.** These are fitted with the usual appliances. One room can be kept at any incubating temperature, and is found on that account to be of very general utility. Owing to the extension of the Hygienic Department, another room, *i.e.*, the old Hygienic laboratory, will be devoted to the study of Bacteriology in connection with the Pathological and Hygienic Departments.

4.—**Photographic Room.** This room contains a micro-photographic and lime light apparatus.

5.—**Animal Accommodation.** This consists in (1) a small caged room in the laboratories which can be kept at a constant temperature, and which is used for monkeys and animals which have been recently operated upon ; (2) a large animal house for reserve stock ; and (3) a calf shed.

6.—**Chemical Room**. This is the most recent addition to the department, and was kindly lent by Professor Ramsay. It is fitted up at the present time to meet the requirements of Dr. Vaughan Harley who will undertake the teaching of this important branch of Pathology.

LIST OF RESEARCHES IN PROGRESS FOR 1892-93.

A large proportion of the work which is being carried out in the Laboratory bears upon the Nervous System, but as will be seen from the following list, Bacteriology and the various other branches of Pathology, claim their number of workers.

NEUROLOGY.

Walter Spencer.—The central innervation of Respiration and of the heart in connection with Shock and Exhaustion.

C. D. Marshall.—Hemisection of spinal cord. Continued from Brit. Med. Jour. 1892. In progress.

Risien Russell.—On some circumstances under which the normal state of the knee jerk is altered. Continued from Proc. Roy. Soc. 1893.

The changes in progressively degenerating muscles. In progress.

Effects of ablation of the cerebellum. In progress.

Cortical representation of eye movements. In progress.

Nusserwanji Surveyor.—(Bombay). Muscle sensory fibres and afferent fibres from the skin. In progress.

Dudley Cooper. Effects of transient and permanent compression of spinal cord. In progress.

A. G. Levy.—The elasticity of the brain substance. In progress.

Otto Lanz.—(Bern). The nature of the muscular tremor in cachexia thyreopriva. In progress,

Eugene Farkas.—(Buda Pesth). A case of microcephaly. Nearly completed.

Rubert Boyce.—Experimental epilepsy. In progress.

The degenerations following extirpation of one cerebral hemisphere. In progress.

Victor Horsley and **S. P. Kramer.**—The effect of gun shot injuries of the brain upon the respiration and circulation. In progress.

GENERAL PATHOLOGY.

Butler Harris.—The reduction of methylene blue in diseased conditions. In progress.

Victor Horsley and **Rubert Boyce**.—On Oedema. Continued from Report, Brit. Med. Jour., 1892.

BACTERIOLOGY.

Rubert Boyce and **Ernest Evans**.—The action of gravity on Bacterium Zopfii. Continued from Proc. Roy. Soc., 1893.

Rubert Boyce and **Nusserwanji Surveyor**..—Madura Disease. Continued from Roy. Soc., 1893; Brit. Med. Jour., 1892; and Path. Soc., 1893.

S. P. Kramer and **Rubert Boyce**.—The action of the serum of vaccinated calves. In progress.

MORBID HISTOLOGY.

Arthur Giles and **Rubert Boyce**.—Cell inclusions in Cancer. Continued from Brit. Med. Jour., 1892, and in Path. Soc., 1893.

PATHOLOGICAL CHEMISTRY.

Vaughan Harley.

1.—Gaseous changes in Pneumonia. Internal and external respiratory changes.

2.—Formation of bile in obstructive jaundice.

3.—Assimilation and digestion in Pancreatic extirpation, etc.

4.—Destruction of sugar in animal economy with special reference to diabetes.

5.—Formation of sugar in the liver.

[*From the* Proceedings of the Royal Society, Vol. 51.]

The Abductor and Adductor Fibres of the Recurrent Laryngeal Nerve.

By J. S. RISIEN RUSSELL, M.B., M.R.C.P.

Communicated by Professor V. Horsley, F.R.S. Received March 17th, 1892.

(From the Pathological Laboratory of University College, London.[1])

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A. Division of the Subject.
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Section 4. (Control) Direct Observation of the Abductor and Adductor Muscles in action after Dissection.
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Introduction.

While engaged in certain experimental investigations in connexion with the cervical nerve roots of the dog ("Roy. Soc. Proc." 1892), the ease with which I found one could separate, in a nerve root, the different bundles of nerve fibres which are concerned with one function from those concerned with another, or even a bundle of nerve fibres destined for the supply of one muscle from one destined for the supply of another, led me to suppose that by exercising sufficient care, it might be possible to separate, in the same way, the abductor from the adductor fibres in the recurrent laryngeal nerve. It is a matter of clincal and pathological experience (Semon,

[1] Part of the expenses connected with this experimental research have been defrayed by a grant from the Scientific Grants Committee of the British Medical Association.

Rosenbach) that in organic and progressive affections of this nerve the abductor fibres are prone to succumb before the adductors; but why this should be so is not at all clear. In like manner, in the well-known experiments of Gad and B. Fränkel[1] on freezing the nerve, the abductor fibres give way before the adductors do. Jeanselme and Lermoyez,[2] by electrical excitation of the laryngeal muscles of human subjects who died of cholera, found that the crico-arytenoideus posticus muscles were the first to lose their excitability after death. This observation has been abundantly confirmed by Horsley and Semon[3] for all classes of animals. On the other hand, ether, reaching the laryngeal muscles through the circulation, puts the adductors into abeyance before the abductors, so that, while excitation of the recurrent nerve of an animal not very deeply under its influence results in adduction of the corresponding vocal cord, similar excitation of the nerve when the animal is profoundly under the influence of the anæsthetic results in adduction of the cord.[4] It seemed, therefore, not unlikely that, if the fibres dominating over the one function could be successfully separated from those dominating over the other, some fresh light might be thrown on this subject.

It is interesting to find that Dr. Felix Semon,[5] in a paper written so long ago as 1881, asked the following question with regard to the fibres of the recurrent laryngeal nerve: "Are we to suppose that, though the nerve is apparently homogeneous, it consists in reality of a bundle of strictly differentiated fibres, bound together simply by a common nerve sheath, and actually differentiated throughout their peripheral course; in fact, having ganglionic centres of their own?" Dr. Semon then goes on to show that the pathological facts strongly support the probability of the truth of this hypothesis.[6]

Morell Mackenzie,[7] in his text-book published the year before Semon raised this question, suggested that possibly the abductor filaments were more superficially situated than the adductor fibres, and that this, if true, would account for the proneness of the abductors to succumb before the adductors in affections, especially compression by tumours, of the nerve. There is, however, no ground for this hypothesis.

[1] *Centralblatt für Physiologie*, May 11th, 1889.

[2] "Arch. de Physiol. normale et pathol," No. 6, 1885.

[3] *British Medical Journal*, Aug. 28th and Sept. 4th, 1886.

[4] Hooper, *Trans. of the Amer. Laryngol. Assoc.*, vol. 7; Horsley and Semon, *British Medical Journal*, Sept. 4th and 11th, 1886.

[5] Semon, "Arch. of Laryngology," 1881, vol. 2, p. 200.

[6] Dr. Semon's views have been amply confirmed by direct experiments on the cortical and bulbar centres for the laryngeal muscles. See history of the subject in paper by Semon and Horsley, *Phil. Trans.*, 1890.

[7] Mackenzie, "A Manual of Diseases of the Throat and Nose," 1880, vol. 1, p. 440.

Since then, the general question of the proclivity of the abductor fibres has been the subject of great controversy, and has been debated both from a clinical and pathological standpoint,[1] but, so far as I am aware, very few attempts have been made to determine the arrangement of the fibres in the trunk of the recurrent laryngeal nerve, either by anatomical observation or direct experimental investigation.

Historical Account of Previous Experimental Researches.

Hooper,[2] wishing to decide, by experimental investigation, whether it is the abductor or the adductor fibres that are really the more prone to succumb in affection of the recurrent laryngeal nerve, passed a thread through the middle of one recurrent nerve, and left it *in situ* in the hope that it would act as a foreign body and excite inflammation of the nerve. At the end of a week, on inspecting the larynx, the vocal cord on the side corresponding to the injured nerve was observed not to come up to the middle line with the same "snap" on expiration as did the cord of the opposite side.

The nerve was found imbedded in a mass of inflammatory tissue, and electrical stimulation of its trunk below this point resulted in abduction of the corresponding vocal cord. When a strong current was used, stimulation of the nerve resulted in abduction of the vocal cord of the same side, and adduction of that of the opposite side. The opposite uninjured nerve was next divided, and adduction of the vocal cord on this side followed stimulation of its peripheral end. Division of the injured nerve below the point at which the thread had been inserted, and stimulation of its peripheral end, resulted in distinct outward rotation of the arytenoid cartilage of that side and an approximation of both arytenoid cartilages at the same time. All attempts to verify these results have failed, so that the experiment stands alone. Proneness of the adductors to suffer before the abductors is what this experiment seemed to point to, but the observer was unable to lay very great stress on this single experiment, positive as it seemed.

The possibility of direct injury to the adductor fibres during the process of inserting the thread into the nerve does not seem to have occurred to this observer, a possibility which is more than likely. Further, it is quite evident that the effects he obtained on the opposite cord, by stimulating the injured nerve,

[1] For a full history of this, see Semon's contribution to the "Virchow-Festschrift;" "Die Entwicklung der Lehre von den motorischen Kehlkopflähmungen seit der Einführung des Laryngoscops," 1891.

[2] Hooper, *New York Med. Journ.*, July 4th, 1885.

were due to diffusion of the electrical current to the nerve of the other side by diffusion to the vagal trunk, and so reflexly to the opposite nerve.

Onodi[1] exposed the muscles of the larynx in dogs, and found that at the point where the recurrent laryngeal nerve crosses the crico-arytenoideus lateralis muscle it splits into three bundles, the first of which supplies the crico-arytenoideus posticus, the second the arytenoideus transversus and crico-arytenoideus lateralis, and the third the thyro-arytenoideus externus. He passed a ligature round each branch, divided all three branches, and then stimulated each separately by an electrical current, and noted the movements of the vocal cords. The communication is an exceedingly brief one; but the observer promised to publish a full account of his experiments later. As far as I am aware, no such publication has appeared up to the present.

These observations can scarcely be said to have thrown much fresh light on the question at issue, as it is only natural to suppose that this nerve, in common with all other motor nerves, should so near its peripheral termination divide into several branches, and that stimulation of each branch of the nerve should evoke contraction of the muscle which it supplies, and thus bring about the particular movement of the vocal cord over which the muscle presides. But this does not at all decide the all important question as to whether the nerve fibres presiding over the different functions have a separate course throughout the entire length of the nerve trunk or not.

Dionisio[2] performed tracheotomy, and then inserted a laryngeal "dynamometer" between the cords. This consisted of a small india-rubber ball, which communicated by means of a tube with a mercurial manometer. The height of the mercurial column during inspiration and expiration was then noted during the natural movements of the vocal cords, its position during expiration being of course higher than during inspiration. The recurrent laryngeal nerve was exposed and stimulated with an electrical current sufficiently strong to produce moderate adduction of the corresponding vocal cord, during which the mercurial column rose. When excitation was discontinued it fell again, and oscillated between the two former points. Circular pressure was then applied to the nerve, commencing with 5 grammes, and going up to 350 grammes, by gradual stages; pressure being kept up for $2\frac{1}{2}$ minutes at each stage. It was found that on stimulating the nerve after each stage there was a gradual diminution in its power of conduction, until stimulation on the proximal side of the point of pressure no longer gave

[1] Onodi, "Berliner Klin. Wochenschr.," 1889, No. 18.
[2] Dionisio, "Arch. Italiani di Laringol.," January, 1892, p. 1.

any response, while stimulation on the distal side resulted in a rise of the pressure, but not nearly so great as formerly. There was a gradual fall of pressure, the inspiratory and expiratory preserving about the same ratio they bore to each other before the pressure was commenced.

Operative Procedure.

Dogs were without exception the animals used in these experiments, and in every case ether narcosis was produced and continued throughout the whole course of the experiment, at the end of which the animal was always killed by an overdose of the narcotic, except in the case of those instances in which it was necessary to allow the animals to live for three weeks, for the study of the degenerations which followed section of certain parts of the nerve. In the latter case the operation, which was always of the most trivial character, was performed under strict antiseptic precautions, and the small wound afterwards treated antiseptically. In every case the small wound healed by immediate union. The animals were narcotised in these, as in the other experiments, and at the end of three weeks death was produced by means of an overdose of chloroform.

Tracheotomy was performed in every instance (except when the animal was to be allowed to live after the operation), a glass cannula being inserted into the trachea. A short rubber tube connected the free end of the cannula with a glass funnel, through which the anæsthetic was administered during the remainder of the experiment. The trachea was then completely divided transversely above the point at which the tube had been inserted. A window was cut from the upper portion of the divided trachea and raised gently, so as to give a full view of the larynx, as seen from below, without producing the least traction on the parts, which might disturb their normal play of movement.[1]

One or other of the recurrent laryngeal nerves was next exposed, separated from the loose connective tissue which surrounds it, and a ligature passed round the trunk of the nerve at the lower part of the neck. The nerve was then divided on the proximal (*i.e.*, bulbar) side of the ligature, and its peripheral end

[1] In observations of this kind it is absolutely essential to view the larynx without traction on the attachments of the cords, since in the dog and the cat traction on the larynx, whether by a ligature directly attached to it, or indirectly by pulling forward the tongue, may most easily produce the appearance of either paralysis or spasm of one vocal cord where no such condition exists in reality.

was separated into its component bundles of nerve fibres, round each of which a ligature was passed and secured.

In the operation for the production of control results by the degeneration method, the nerve, after being exposed and separated from the surrounding connective tissue, was placed *in situ* upon a piece of cork, in order to steady it, and one bundle of nerve fibres being carefully separated from the others which compose the nerve, a few millimetres of this bundle were excised. These operations were performed under strict antiseptic precautions, the wounds closed by continuous aseptic silk sutures, and afterwards dressed antiseptically, healing by first intention, tracheotomy not having been performed.

Division of Subject and Analysis of Results.

A. *Division of Subject.*

The first part of the following research consists in the separation and isolation of the different bundles of nerve fibres of which the nerve trunk is composed, electrical excitation of each separate bundle, and observation of the effects produced on the vocal cords by such excitation.

Exposure of the different bundles of nerve fibres under exactly similar circumstances to the drying influence of the external air, with observation of the relative duration of vitality possessed by the different bundles, forms the second part of the investigation.

Other methods were next instituted to control the results of the foregoing, and the first of these, constituting the third part of this work, consisted in tracing by *post-mortem* dissections each bundle of nerve fibres separated in the nerve trunk to its termination in the mucous membrane or in a muscle of the larynx.

The next control method consisted in exposing the muscles of the larynx immediately after death, and direct observation of them during excitation of the separate bundles of nerve fibres, this being controlled by occasional excitation of individual muscles themselves. This forms the fourth part of the investigation. The fifth or last part of the research served as a third control method, and consisted in observations of the muscular degenerations which followed division of one or other bundle of nerve fibres in the nerve trunk, three weeks after such division.

B. *Analysis of Results.*

Section 1. *Separation and Excitation of the Individual Bundles of which the Nerve is composed.*—The separation was brought about by means of an exceedingly delicate thin-bladed knife. The divisions between the different bundles of fibres

could usually be seen by the naked eye, and further guides were the minute capillary twigs which usually course on the surface of the nerve along these lines of division. When no such guides could be seen by the unaided eye, a lens was used to assist in their recognition. Great care was taken to preserve the vitality of the nerve fibres by constantly bathing them with warm normal saline solution. Each bundle was in turn raised into the air, and stimulated by means of fine platinum electrodes attached to the secondary coil of a du Bois-Reymond's inductorium, supplied by a bichromate cell. The same strength of current was used for all the bundles of nerve fibres in any given experiment, and was on an average 5,000 to 7,000 on Kronecker's inductorium scale; and the rate of interruption was 100 per second. The results in twelve dogs showed that excitation of certain bundles produced no effect on the vocal cord, while excitation of others produced abduction or adduction of the vocal cord on the same side, according to the bundle of fibres stimulated; and, as far as could be ascertained, those fibres, excitation of which produced abduction of the cord were situated internally to those which produced adduction, *i.e.*, the former are situated on the side of the nerve next to the trachea. But of this point it is difficult to be absolutely certain, as the difficulties of preserving the nerve in its normal position during the investigation are very great.

Section 2. *Relative Vitality of the respective Bundles.*—It was found that if the bundles of nerve fibres were separated, as has been already explained, and the abductor and adductor bundles of fibres thus isolated placed upon a piece of cork, and left exposed to the air of the room under exactly similar circumstances, the abductor fibres ceased to conduct impulses in response to electrical excitation long before there was the slightest sign of similar failure on the part of the adductors. The same strength of current and the same number of interruptions per second were employed in each case, with the result that the abductor fibres ceased to conduct impulses in about twenty to thirty minutes, on an average, after transverse section of the nerve and separation of its component bundles; while the adductor fibres would continue to conduct impulses well for three hours and more.[1]

That this death of the abductor fibres did not take place throughout the whole length of the nerve at the same time is proved by the fact that when the portion under observation ceased to conduct impulses, an effect could be often produced by stimulating some portion of the bundle

[1] The experiment was never continued longer than a little over three hours, as there seemed no necessity for it.

situated nearer the peripheral end of the nerve, until at last even stimulation of the nerve ends in the muscle failed to produce any effect. The adductors meanwhile acted well to the original strength of stimulus, even when applied to the original seat of separation of the bundles. As is well known, if all the fibres of the recurrent laryngeal nerve be stimulated simultaneously in the adult dog, adduction of the vocal cord results; while the same procedure in the young dog results in abduction of the vocal cord. (See all previous observers, from Legallois to Semon and Horsley.) In such young animals, even after separation of the different bundles of nerve fibres in the trunk of the nerve from each other to the extent of an inch to an inch and a-half, it is at first impossible to get any other effect than abduction of the corresponding vocal cord. But there comes a time when stimulation of one of the separated bundles results in abduction, while stimulation of another results in adduction. Still later the abductor bundle ceases to produce this effect when stimulated with a moderate strength of current, and when a very strong current is used adduction of the vocal cord follows, as in the case of stimulation of the other bundle of nerve fibres. The explanation of these phenomena seems to be that in the young dog the abductor fibres are more excitable than the adductors, so that a strength of current short of that necessary to evoke action of the adductor muscles diffuses to the abductor fibres, which, being more excitable, cause abduction of the vocal cord; but that, as in the adult animal, the tendency to death of the abductor fibres is more marked than that of the adductors, so that there comes a time in the young animal when the abductor fibres have so far lost their excitability that stimulation of the adductor bundle with a current strong enough to evoke contraction of the adductor muscles, though it still diffuses to the abductor fibres, is no longer capable of exciting them, and in the end the abductor fibres lose completely their excitability, while the adductors, though relatively less excitable in the beginning, preserve their excitability, even in this case, longer than the abductors, which on their part preserve it much longer than in the adult animal.

Section 3. (*Control*) *Tracing the respective Bundles to their Peripheral Terminations by Dissection.*—Having ascertained by electrical excitation the functions subserved by the different bundles of nerve fibres in the nerve trunk, these bundles were traced *post mortem* by careful dissection to their peripheral terminations. All the bundles of nerve fibres were thus dealt with, but the present research does not make it necessary for a description to be given of any but the motor fibres. From several such dissections, taken together with the facts ascertained during the excitation experiments, it seemed almost

certain that the abductor bundle of nerve fibres is situated on the inner side of the nerve, *i.e.*, next to the trachea, while the adductor bundle is situated on the outer side of the nerve. The abductor bundle may be traced to the crico-arytenoideus posticus muscle on the same side, and to it alone, none of the fibres to the adductors being contained in this bundle; while the adductor bundle supplies branches to all the adductor muscles on the same side, and to the arytenoideus.

Section 4. (*Control*) *Direct Observation of the Abductor and Adductor Muscles in Action after Dissection.*—In six dogs the nerve was exposed at the lower part of the neck, and the different bundles of fibres separated. The nerve fibres were carefully preserved by being covered with a piece of cotton wool saturated with warm normal saline solution. The animal under observation was then killed by an overdose of chloroform, the larynx quickly excised, and its muscles exposed by dissection.

By this method, on excitation of the nerve fibres not only could the movements of the vocal cords be seen, but also the contraction of the muscles directly engaged in bringing about the movement of abduction or adduction, as the case might be. These observations showed that so perfectly could the nerve fibres concerned with the one function be separated from those concerned with the other, that stimulation of the one set evoked contraction of the abductor muscle alone, while stimulation of the other set evoked contraction of the adductor muscles alone.

Section 5. (*Control*) *Degeneration Method.*—The difficulties which attended this group of experiments were very great.

An attempt was made to separate one bundle of nerve-fibres from the others, and to excise a few millimetres of it without injuring the other bundles contained in the nerve trunk, and, of course, without severing the whole nerve trunk. As can be easily understood, the ease with which damage can be done to so delicate a nerve is very great, and in the absence of any means of fixing the nerve (such as was afforded by the ligature in the excitation experiments) without producing damage to any but the bundle of fibres that were to be eliminated, the nerve trunk rolled about so freely that the task was attended by endless difficulties. It is, therefore, scarcely surprising that, out of seven experiments, the results were unsatisfactory in three instances. But those that were successful yielded such striking results that, in view of the great difficulties attending them, further multiplication of these experiments has been considered unnecessary. In one instance, the adductor fibres in the nerve trunk were successfully separated, and a few millimetres excised. As in all these experiments, the wound healed

by primary union; and when the dog was killed, three weeks after operation, the autopsy revealed the following:—The adductor muscles on the side of the damaged nerve were atrophied and degenerated, while the abductor muscle of the same side was normal, as were naturally all the muscles of the opposite side of the larynx.

In two instances the abductor fibres were successfully divided without injury to the adductor fibres. During life in one case, there were feeble attempts at abduction during vigorous inspiration, and in the other there were not the slightest signs of abduction. In both cases the autopsy revealed atrophy and degeneration of the crico-arytenoideus posticus on the side corresponding to that of the injured nerve, while the adductor muscles of the same side and all the muscles of the opposite side of the larynx were normal. In all these three cases direct electrical excitation of the muscles confirmed the conclusions which had already been come to by observing their loss of function and degenerate appearance. In the fourth case, as was supposed at the time of the operation, owing to their position, the bundle of fibres divided was evidently not one of those supplying the muscles of the larynx. Three weeks after the operation the vocal cord on that side performed its excursions perfectly normally, as did that of the opposite side. Separation of the abductor and adductor fibres was then effected in the remainder of the nerve trunk, and excitation of these bundles evoked their respective movements of the vocal cord on the same side. Finally, on *post-mortem* examination in this case, none of the muscles on either side of the larynx were found atrophied or degenerated. It consequently served as a gratifying control of the other degeneration experiments.

Summary and Conclusions.

The results of these experiments show clearly:—

1. That the abductor and adductor fibres in the recurrent laryngeal nerve are collected into several bundles, the one distinct from the other, and each preserving an independent course throughout the nerve trunk to its termination in the muscle or muscles which it supplies with motor innervation, a condition of things the possibility of which was suggested by Dr. Semon more than ten years ago, from the evidence of pathological facts.

2. That while in the adult animal simultaneous excitation of all the nerve fibres in the recurrent laryngeal nerve results in adduction of the vocal cord on the same side, abduction is the effect produced in a young animal by an exactly similar procedure.

3. That when the abductor and adductor fibres are exposed to the drying influence of the air under exactly similar circumstances, the abductors lose their power of conducting electrical impulses very much more rapidly than the adductors, in other words, they are more prone to succumb than are the adductors, a fact which has for long been recognised and insisted on by Dr. Semon as being the case in the human subject, and in support of the truth of which that observer has adduced so many powerful arguments.

4. That, even in the young dog, the abductor nerve fibres, though preserving their vitality much longer than in the case of the adult animal, nevertheless in the end succumb before the adductor fibres.

5. That this death commences at the point of section of the nerve, and proceeds gradually to its peripheral termination, and does not take place in the whole length of the nerve simultaneously.

6. That it is possible to trace anatomically the abductor and adductor fibres throughout the whole length of the recurrent laryngeal nerve to their termination in the one or other group of laryngeal muscles, and that these fibres appear to bear a fixed relationship to each other throughout their course, the abductors being situated on the inner side of the nerve or that next to the trachea, while the adductors are on the outer side.

7. That it is possible to so accurately separate these two sets of fibres in the nerve trunk that excitation of either of them evokes contraction of the abductor or adductor muscles, as the case may be, without evoking any contraction whatever in the muscle or muscles of opposite function.

8. That the bundle of nerve fibres concerned with one function may be divided without injury to that concerned with the opposite function, and that such division is followed by atrophy and degeneration of the muscles related to that function without any such changes being detectable in the muscles related to the opposite function.

Further, it was clear that the theory advanced by Mackenzie, and which has since found favour with many, viz., that possibly the reason why the abductor fibres succumb before the adductor in affections of the nerve is because they are more superficially and circumferentially arranged, while the adductor fibres are situated deep in the substance of the nerve, is shown by these experiments to be entirely erroneous.

One point which is difficult to explain is why there should be so marked a difference between the recurrent laryngeal nerve of a young and that of an adult dog, as regards the respective predominance of abductor or adductor representation in the trunk of the nerve. Possibly the reason why the

abductor influence is in the ascendancy in the young dog is because the power of phonation is still imperfectly developed, and with it both the muscle and nerve fibres subserving this function are also imperfectly developed, while the function of respiration is from the beginning fully developed, and with it the muscle and nerve fibres connected with that function. That the reverse should be the case in the adult animal may well be due to the fact that phonation is perfectly developed, while respiration has become so automatic that very feeble stimuli are necessary to keep it going.

My sincere thanks are due to Professor Victor Horsley for allowing me to carry out this research in the Pathological Laboratory of University College, London, and for being so good as to verify the results which I obtained from time to time.

I wish also to express my thanks to Dr. Felix Semon for having very kindly given me access to his valuable collection of literature on the subject, and facilitating the work of writing this paper.

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THE BACTERIOLOGY

OF

EPIDEMIC EXFOLIATIVE DERMATITIS.[1]

BY J. S. RISIEN RUSSELL, M.B., M.R.C.P.

I WISH to express my sincere thanks to Dr. Savill for his kindness in giving me the opportunity of carrying out the following investigations in connection with the epidemic skin disease, the clinical and pathological characters of which have already been so ably discussed by him; and also for his courtesy in putting every facility in my way while I was engaged in these researches. Unfortunately the opportunity only came towards the end of the epidemic, so that the amount of material at my disposal has been limited, though sufficient, I think, to warrant the conclusions I have come to, which are stated in the concluding paragraphs of this paper.

General plan of research.—1. The skin of patients suffering from the disease was examined microscopically for micro-organisms.

2. Artificial nutrient media[2] were inoculated with blood which was withdrawn from the bodies of such patients, during life in some cases, and after death in others.

3. The under surface of flakes of epithelium, detached from the bodies of patients, was also employed for inoculating artificial nutrient media.

4. The broth culture was used to inoculate gelatine, from which plate cultures were made in order to separate the colonies; and from

[1] From the Pathological Laboratory of University College.

[2] In all such inoculations broth was the nutrient medium employed.

such separated colonies pure cultures were made on gelatine, agar-agar and potato.

5. From such pure cultures cover-glass preparations were made, and various colouring agents used to bring the micro-organism into evidence.

6. Animals were inoculated with pure cultures of the organism.

7. Finally, control experiments were made. (*a*) Sections of skin of patients who were not subjects of the disease were prepared and stained for organisms, exactly as had been done with the sections of skin from patients suffering from the disease. (*b*) Artificial nutrient media were inoculated with the blood taken from the cavities of the hearts of patients who had died of some other disease.

Microscopic examination of the skin.—Specimens were obtained by excising small pieces of skin the surface of which had been carefully purified by being washed with solution of perchloride of mercury (1-1000), and afterwards well rubbed with absolute alcohol. The specimens were cut in gum, and the sections afterwards stained in the following ways:—(1) Methylene blue, watery solution; (2) gentian violet, alcoholic solution; (3) fuchsin, alcoholic solution; (4) Gram's method, stained with gentian violet, and decolourized by Gram's solution; (5) Weigert's method, picrocarmine used as the ground stain for the tissue, and gentian violet as that for the micro-organisms.

The prevailing micro-organism found in sections prepared in all these various ways was invariably a diplococcus, though a few cocci were also found, and in one specimen a single chain of streptococci. These diplococci were scattered through the sections, and were especially numerous in the deeper layers of the skin.

Cultivations from the blood.—(*a*) *Taken from patients during life.*—The surface of the skin was carefully cleansed with perchloride of mercury (1-1000 sol.), the part chosen being free from exudation or suppuration. A small puncture was made with the point of a knife the blade of which had been well heated in the flame of a spirit lamp; and the blood collected in capillary tubes which had been previously hermetically sealed and sterilized. The tube was run several times through the flame of a spirit lamp after one of its closed ends had been broken off. After the blood had been collected in it, its point was again hermetically sealed by keeping it in the flame of the spirit

lamp for a few seconds. The blood thus obtained was next put into broth, and at the end of twenty-four and forty-eight hours, other media were inoculated from the broth, including gelatine plates for the separation of the colonies. These experiments were only carried out in connection with three different patients: once the result was negative, once septic organisms were present,[1] and once staphylococcus aureus was the only organism present.[2] Through the kindness of Dr. J. J. Pringle, I had an opportunity of examining the blood of a fourth patient who was under his care in the Middlesex Hospital, and who was at the end of the fifth week of what was diagnosed to be a sporadic attack of this disease; but this examination also yielded a negative result. Possibly in all these cases the blood was not examined early enough in the course of the disease; in one case it was examined as late as the fourteenth week.

(*b*) *Blood taken from the cavities of the heart after death.*—I had not an opportunity of obtaining the blood myself, but Dr. Savill informs me that he took the following precautions when securing it:—The heart was rapidly removed and plunged whole in a strong solution of mercuric chloride (about 1 in 100) and left there for 10-15 minutes. Then it was removed, and a hole made into the left ventricle with a sterilized scalpel, through which carefully sterilized capillary tubes were plunged, allowed to fill, and immediately sealed in the flame of a spirit lamp. In all such cases the specimens of blood were set aside for two or three months before being used. Then the same routine was gone through as in the last set of experiments; and cultures were obtained, from which cover-glass preparations were made. These were stained with gentian violet, and on microscopic examination the organism proved to be a diplococcus, identical in appearance and behaviour to that already seen in the sections of the skin, *e.g.*, a patient (M. XXV.), died with the disease fully developed, and the blood from the left ventricle contained this micro-organism, *and it alone*. In one instance the blood was found to be swarming with septic organisms when the cultures were made from it. This

[1] In this case the blood had been kept for several weeks before the cultures were made.

[2] The skin of the part punctured, though carefully cleansed, had been exuding a slight purulent discharge previously.

was no doubt due to the accidental entry of such organisms at the time when it was obtained, or possibly before this.

Cultures from the under surface of epithelial flakes removed from patients who were desquamating.—The scales chosen were such as had not yet become detached. The outer surface of these was carefully rubbed with perchloride of mercury (1-1000 sol.), and then with absolute alcohol. By means of a pair of sterilized forceps flakes were then raised, and some put into broth, while the under surface of other flakes was rubbed over the surface of gelatine. In twenty-four hours, at a temperature of 20° to 25° C., very small white colonies, scarcely visible to the naked eye, were to be seen scattered on the surface of the gelatine, and in forty-eight hours they became quite distinct. They were uniformly of the same appearance, and sub-cultures on gelatine, from different colonies, all presented exactly the same appearance. From the broth cultures were made on other media, at the end of twenty-four and forty-eight hours; and in every case they were identical with those obtained from the gelatine colony cultures. Microscopic examination of cover-glass preparations made from the various cultures showed them to consist of the diplococcus which had been found in the sections of the skin, and in the cultures obtained from the blood. Plate cultures were made, and all the colonies seem to be identical in appearance. Among the numerous micro-organisms present in cultures from epidermic flakes from Dr. Pringle's case, already referred to, the characteristic diplococcus was conspicuous by its absence.

Inoculation experiments.[1]—Pure cultures of the organism were mixed with distilled water in such quantity that the mixture was quite opaque and milky. Of this 2 C.C. were inoculated into one guinea-pig, and twice that quantity into another; the subcutaneous tissue of the abdominal wall being the site chosen for the inoculation in each instance. The animals never showed the slightest sign, either locally or constitutionally, that there was anything wrong with them.

The ear of a rabbit was shaved, and then scratched until it became rough and excoriated; some of a pure culture of the organism was then rubbed well in, but the animal never showed any sign of being affected either locally or constitutionally. Another rabbit was inocu-

[1] I am indebted to Mr. Rubert Boyce for having kindly inoculated the animals for me, as I do not hold the necessary certificate.

lated by subcutaneous injection with 4 C.C. of a broth culture, with absolutely no result. A young dog was similarly treated with a similar amount of broth culture, with a like negative result.

Control investigations.—(*a*) Sections of skin, from persons not suffering from the disease, were stained in exactly the same way as were those taken from patients suffering from the disease, in order to determine whether or no the same micro-organism is to be found in such healthy skin. The results of these examinations showed that such skin does not contain these micro-organisms.

(*b*) Artificial nutrient media were inoculated with blood taken from the cavities of the hearts of patients who died of some other disease, and who had never suffered from the disease in question, but no cultivations could be obtained from such blood.

(*c*) I had the good fortune to obtain the opportunity of examining the blood of a typical case of Pityriasis rubra which was under the care of Dr. J. J. Pringle in his private practice. The patient was in the fifth week of the disease, and inoculation of various nutrient media with the blood failed to demonstrate the presence of any micro-organisms.

Characters of the micro-organism.—It is a diplococcus,[1] in size almost as large as Friedländer's diplococcus of pneumonia. Its segments are either ellipsoidal or rod-like, according to the stage of its development. Attempts to bring into evidence a capsule have never succeeded. It is easily stained by all the usual colouring matters, and is not decolourized by Gram's solution. As has already been said, it may be brought into evidence in the tissues by Weigert's double stain. The stain that it takes on most readily is an alcoholic solution of gentian violet, while that which it takes on least readily is a watery solution of methylene blue. It grows readily in all the various artificial nutrient media, at the ordinary temperature, but most rapidly at a temperature of 20° C. In broth it settles at the bottom of the vessel as a whitish mass, which, when shaken up, rises in long shreds. The upper portion of the liquid is also made opaque. At the ordinary temperature it does not show signs of commencing

[1] The term *diplococcus* is used loosely to denote the paired arrangement of the segments, and is only applicable to this organism in the sense in which it is used to denote Friedländer's organism, which consists in reality of short rods lying singly or in pairs.—*Cf.* Fraenkel, "Grundriss der Bakterienkunde," Berlin, d. auf, p. 411.

to grow for several days; but at a temperature of 20° to 25° C. there is distinct evidence of commencing growth at the end of twenty-four hours, which has increased greatly by the end of forty-eight hours. On gelatine it commences to grow in twenty-four hours at a temperature of 20° to 25° C., and in its earliest stage appears as very minute round colonies, almost identical in appearance to a culture of the streptococcus of erysipelas. At the end of forty-eight hours it has lost this character, owing to the blending of the colonies to form a uniform slightly-raised growth with even borders, in which condition it remains for a few days, with the exception of becoming a little thicker. It has a distinctly bluish-white colour, and is slightly fluorescent. After a few days it ceases to become thicker, but spreads slowly and irregularly at its margin, so as to produce a much broader culture, with sinuous edges. *It does not liquefy gelatine,* and it requires oxygen to enable it to flourish, as may be readily seen by its behaviour in "stab cultures." In these it grows in the form of minute white round colonies all along the tract of the needle, but in diminishing size and number as the lowest part of the tract is reached, while on the surface it spreads itself out as a flat, uniform, bluish-white disc, the diameter of which is about a sixth to a quarter of an inch or more. In gelatine plate cultures it appears as minute white points, scarcely visible with the naked eye at the end of twenty-four hours, but in forty-eight hours they become quite distinct. These colonies always remain of small size, are spherical, and have even edges. When deep in the gelatine they preserve these qualities, but when on the surface there appears to be a tendency for them to become fluffy. On agar the cultures present no special features worthy of note, but on potato the growth is exceedingly luxuriant, greatly heaped up, and is of cream colour. It grows at exactly the same rate as on gelatine, at a temperature of 20° to 25° C.

Summary and Conclusions.—We have therefore to deal with an organism which is found in the skin, blood, and exudations of patients suffering from this epidemic skin disease; which is stained by all the ordinary colouring matters; which grows readily on the artificial media of cultivation; which grows better in the presence of oxygen than without it; which does not liquefy gelatine; and which, when inoculated into animals, in the

doses that have so far been tried, has produced no effect, except in one instance; but in this case Dr. Savill succeeded in communicating the disease to a rabbit, from whose blood typical cultures of the same organism were made, and verified to be such by microscopic examination.

The constancy with which this organism is found in connection with the subjects of the epidemic skin disease forbids my believing that its presence is merely accidental; at the same time, as a specific effect on animals has only once been obtained, I am not in a position to affirm that it is the cause of the epidemic disorder which we are considering. Nevertheless, it seems to me that there are ample grounds for suggesting that probably such an ætiological relationship between the organism and the disease does exist. While any specific effect on several animals, resembling that met with in man, would render this ætiological relationship certain, the absence of such effect does not preclude all possibility of the relationship; for we are well aware that other diseases depending on specific organisms exist in man, which up to the present have not been able to be communicated to the lower animals. And we are justified in hoping that, as one animal proved susceptible to the effects of the micro-organism, inoculation of other animals will be attended by additional positive results, instead of the negative ones that have been so far obtained.

As to whether the organism is one which has not been previously described is a question the solution of which would require far more space than can be devoted to it in a paper of this kind; but the main point which we have to decide is not whether or no the organism has been previously described, but whether it is or is not the cause of the disease, the contagiousness of which Dr. Savill has so clearly established. Although this is so, I nevertheless feel that it may not be altogether out of place to call attention to the points of difference which exist between this micro-organism and that which it most resembles in its character, and the conditions under which it is found —viz., the Staphylococcus pyogenes albus. Without going uselessly into detail with regard to minute and possibly contestable differences, the following striking ones will, I think, serve to show that the two organisms are by no means the same:—

1. The organism under consideration is a diplococcus (in the sense indicated), whose segments are ellipsoidal or rod-like, while Staphy-

lococcus pyogenes albus exists as cocci, diplococci, masses of cocci, and chains.

2. It does not liquefy gelatine, while Staphylococcus pyogenes albus does so rapidly.

3. It does not appear to produce a specific effect on animals with the same ease or certainty as the Staphylococcus pyogenes albus.

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[*From the* Proceedings of the Royal Society, Vol. 51.]

AN EXPERIMENTAL INVESTIGATION

OF THE

Nerve Roots which enter into the Formation of the Brachial Plexus of the Dog.

By J. S. RISIEN RUSSELL, M.B., M.R.C.P.

Communicated by Professor Victor Horsley, F.R.S. *Received Feb.* 18, 1892.

(From the Physiological Institute of Berlin and the Pathological Laboratory of University College, London).

(Abstract.)

The subject is introduced by an allusion to the attempts that have been made by anatomists to determine the functional relationships between the nerve roots and groups of muscles they supply, in which connection the work of Krause, Schwalbe, Herringham, and Paterson are cited. A brief reference is made to the observations of Erb, Duchenne, Knie, and Thorburn, after which the author refers to the experimental work that has been done in this field by Müller and Van Deen, Kronenberg, Panizza, Peyer, Krause, Ferrier and Yeo, Bert, Marcacci, and Forgue. The anatomical accounts of the brachial plexus of the dog as given by Ellenberger and Baum, Chauveau and Arloing, and Forgue are quoted, the discrepancies which exist between these different accounts pointed out, and the author's own experiences in this connection, differing in some points, while agreeing in others, with the descriptions given by these observers, are detailed.

He then proceeds to explain his methods of experimentation, which consist in :—

1. Observation of the compound movements in the fore limb of the dog by electrical excitation of the peripheral end of the whole of a cervico-brachial nerve root which had been previously exposed and divided.

2. Minute differentiation obtained by electrical excitation of the individual bundles composing such a nerve root.

3. Direct observation (after dissection) of the muscles thrown into action by electrical excitation of the separate nerve roots. As a corollary to this, the question as to whether or no a single bundle of fibres representing a single simple movement in a nerve root ever remains distinct in its course to the muscles it supplies, without inosculating with other nerve fibres, is dealt with. A further point determined is whether, when a muscle receives nerve fibres from more than one cervico-brachial nerve root, both nerve roots supply fibres to one and the same muscle fibre or not.

4. Alteration in the action of the fore limb in progression or in standing, evoked by section of a nerve root or roots.

5. Influence of section of a root or roots in excluding part of a generalised epileptic spasm induced in the limb by cortical excitation.

6. Differentiation of parts of the nerve roots by the degeneration method, in which connection an allusion is made to certain results obtained by the author, which do not accord with the Wallerian law of degeneration, and which are in accord with the experiments of Joseph.

From the results of these various methods of experimentation, the author draws the following conclusions :—

I. *Stimulation Experiments.*

1. The compound movement obtained by stimulation of a whole nerve root is a well-coordinated one, depending on the action of a group of muscles in synergic combination, as Ferrier and Yeo showed to be the case in the monkey.

2. This compound effect may be resolved into its component factors when it is found that movements diametrically opposed to each other may be represented in the same nerve root, *e.g.*, flexion and extension.

3. Such single simple movements bear a constant relation to the nerve roots, the same movements being always found in any given root, and thus such movements always bear the same relation to the spinal level ; *e.g.*, flexion of the elbow is always represented one root higher than extension of the same joint.

4. Fibres representing a certain movement always preserve the same position in a given nerve root; *e.g.*, extension of the wrist is represented by a bundle of fibres in the upper part of the circumference, while flexion is represented by a bundle of fibres in the lower part of the same root.

5. Each bundle of nerve fibres representing a single simple movement in a nerve root remains distinct in its course to the muscle or muscles producing such a movement, without inosculating with other motor nerve fibres.

6. The group of muscles supplied by any given nerve root occupy both the anterior and posterior surfaces of the limb. In other words, muscles whose unimpeded action would produce one movement are represented in the same root as others whose action would produce a movement diametrically opposite.

7. In such combinations certain muscles are always more extensively represented than others, so that, with a current sufficiently strong to stimulate all the fibres of a nerve root equally, certain muscles predominate in their action over others.

8. The muscles whose action predominates in one root always predominate in that root.

9. If the muscles producing flexion of a certain joint predominate in their action in one root, those producing extension predominate in another.

10. It is possible, by stimulation of a single bundle of fibres in a nerve root, to produce contraction of a single muscle, and it alone.

11. The same muscle is always represented in more than one nerve root, usually two, and to an unequal extent in these.

12. When the same muscle is represented in two nerve roots, the muscle fibres innervated by one root are not innervated by the other.

II. *Ablation Experiments.*

1. Division of any given nerve root produces paresis of the group of muscles supplied by it.

2. This paresis is only temporary, and soon passes off almost completely.

3. Such division of a nerve root does not result in incoordination of the remaining muscular combinations represented in other nerve roots.

III. *Exclusion of a certain Root or Roots during an Epileptic Spasm in the Limb (the root being divided at the time, and not some time previously).*

1. Division of one or more nerve roots produces alteration of the position of a limb during an epileptic spasm, which altered position depends on the particular muscular combinations that have been thus thrown out of action.

2. No incoordination is produced in the action of the remaining muscular combinations.

3. There is no evidence of overflow of the impulses which ought to travel down the divided root into other channels through the spinal centres, so as to reach the muscles by new paths.

IV. *Degeneration Method.*

1. These experiments confirm the anatomical facts that had been previously ascertained by dissection, as to which nerve roots supply any given nerve with fibres.

2. The degeneration which results in the nerves is not a scattered one, but is localised to distinct bundles of nerve fibres occupying a certain position in the transverse section of the nerve.

3. The Wallerian law of degeneration is found to be erroneous with regard to the degenerations which result on division of a nerve root on the distal side of the intervertebral ganglion; for not only is degeneration found in the peripheral end of such a root, but also in that portion of the sensory root between the ganglion and the spinal cord; pointing to the probability that there are certain nerve fibres which do not depend on the ganglion for their trophic supply, but derive the same from elsewhere, either the spinal cord at another level, or the periphery.

In conclusion, the author calls special attention to the value of the method of excluding one or more nerve roots during an epileptic spasm, as affording a means of confirming the facts that have been previously observed from stimulation of the nerve roots. and also of ascertaining new facts with regard to them and the plexuses which they form. He further goes on to point out that it supplies a valuable means of studying the manner in which conduction of impulses from the cortex through the nerve roots and plexuses to the muscles takes place; and that it is capable of still wider extension, as if, instead of producing general epilepsy, less powerful stimuli be applied to the centres for different movements, as represented in the motor cortex, it will afford a means of connecting such centres, or parts of these, with the nerve roots to which fibres proceed from these cortical motor centres.

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On the Factors which produce Septic Peritonitis.

Being a Report to the Scientific Grants Committee.

By MAX WALTHARD, M.D., M.R.C.S.Eng., of Bern.

(From the Pathological Department, University College, London).

THE question as to how far the peritoneum in a normal state is able to resist infection, and the further question what are the factors which go far to inhibit its powers of resistance, still await answer. It was principally with the object of answering the latter inquiry that the following investigation was undertaken. I may here say that a paper by myself on the subject, dealing with the history of previous experimental research, will shortly be published in the *Archiv für klinische Chirurgie*. Since in all laparotomies the peritoneal cavity is opened and the peritoneum exposed to the air, the first point to investigate was that to which Delbœuf has already devoted much attention—namely, the influence of simple exposure. Exposure involves of necessity the following conditions, all or each of which may be an injurious factor—drying, cooling, "irritation." The latter term is used to denote any theoretical effect which the atmospheric gases may be supposed to exert on the peritoneum. To answer the general question first, the following arrangement was adopted :

In almost all cases rabbits were the animals employed, and were narcotised with ether. All instruments were, of course, sterilised by boiling, the field of operation suitably guarded by an apron, and the abdomen closed by the continuous suture.

Experiment A.—The abdominal cavity was opened, and a moderate area of peritoneum kept exposed for fifteen

minutes. The cavity was then infected with a pure culture of pyogenic micro-organisms, and the wound closed.

Experiment B.—The opening in the abdominal cavity was covered by a glass-domed cylinder, the top of which was perforated to allow of a chemical thermometer being inserted, and the sides of which were provided with tubulures and glass taps to permit the cavity of the cylinder to be filled with any required gas or vapour. An identical area of serous membrane being exposed, and the cylinder placed over it, steam was admitted into the latter, and the preparation thus kept moist and at a temperature of 40° C. for fifteen minutes. Finally it was, as in the first case, infected.

The result of such parallel experiments was that in A peritonitis occurred; in B it was absent. The next step was to differentiate between the factors before enumerated. By means of the simple apparatus just referred to, the peritoneum was exposed under the previously-mentioned plan to steam at 40° C, with the respective admixture of oxygen, carbonic acid, and nitrogen, and, finally, infection. In no case did peritonitis occur.

It is clear, therefore, that desiccation is the most important adjuvant factor in peritonitis. The practical conclusion to be drawn is that in all laparotomies the parts exposed should be freely irrigated with sterilised warm normal saline solution. Concerning the formation of adhesions several points are well worthy of investigation, since an ideal condition of the peritoneum after an operation should of necessity exclude the presence of adhesions.

The conclusions I am able to draw from my experiments are as follows :—

(1) In an aseptic and "protected" (that is, by warmth and moisture) operation, with or without infection, no adhesions form between an injured surface if that is opposed to a normal one. Thus the abdominal cicatrix is not adherent to omentum nor bowel, and the serous covering of the bladder or uterus may be freely destroyed by the cautery, without any adhesion forming between it and the neighbouring structures covered with normal membrane.

(2) If two injured surfaces are free to move in the cavity, that is, by peristalsis, &c., no adhesion forms. The reason of this is that each injured surface moves opposite an uninjured area. That this is actually the case I have

shown by immobilising the bowel by (*a*) giving opium after the operation (*b*) fixing the parts by a ligature, and finding that under these circumstances adhesions invariably presented themselves. The empirical objections to opium after laparotomy thus find a basis in fact from the point of view of preventing adhesions.

As regards the freedom of movement, I should add that the force of peristalsis is sometimes sufficient to detach a silk suture uniting the sides of two coils of intestine.

Summary.

(*a*) During laparotomy, the peritoneum must be kept wet and warm.

(*b*) In cases in which adhesion of serous surfaces is to be avoided, opium should not be given.

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ON A NEW MICRO-ORGANISM OF SPREADING ŒDEMA.

By A. Butler Harris, M.A., M.B., B.S. (Oxon.), (*Prize Essay for the Liston Gold Medal, University College, London*, 1892).

From the Pathological Laboratory of University College, London.

The following is a brief history of the case in which the organism, presently described, occurred:—

Ellen Owen, housewife, æt. 38, married, was admitted to University College Hospital, on November 21st, 1891, under the care of Dr. Bastian, in a semi-conscious condition. She complained, on questioning, of pain behind the right ear, over the front and back of the head, and of general prostration.

The history of the case was briefly as follows:—

Four months before admission (in August) she had an attack of influenza. This lasted a fortnight; she recovered, but was left with a foul-smelling discharge from the right ear, accompanied by violent pains in that ear, with deafness. She had had no previous ear trouble.

For the next two months she had several periods of improvement, and relapse, with severe pain in the head. On November 1st, three weeks before admission, there was an exacerbation of pain in the right side of the head. A week later her friends noticed that her face was drawn over to the right side, and that she seemed weak on the left side of the body. She was able to walk about until November 16th, when she took to her bed. For six weeks she had had vomiting without any feeling of nausea. Two days after taking to bed (November 18th), she became drowsy, stupid, and finally, delirious.

On admission, November 21st, she was found to be hemiplegic and rigid on the left side, with paralysis of the left side of the face. Localisation of sensation was imperfect, and the sphincters were not under control. There was no marked optic neuritis. The temperature was 101° F.

The head was turned slightly to the right, and the right hand was raised to the forehead.

The next day, Mr. Horsley trephined at a point just behind, and on a level with the upper border of the squamous suture, on the right side. The dura mater bulged from tension, and was opened. Pus was found when the seeker was introduced into the brain in a downward direction. A second counter trephine opening was made further forwards, and at a slightly lower level. A free opening was thus made in the temporo-sphenoidal lobe, tubes were introduced, and the abscess irrigated with 1 in 4000 perchloride of mercury.

The pulse improved as soon as the intracranial tension was relieved by evacuation of the pus.

Later in the day it was noticed that the paralysis of the left arm was less,

and that the rigidity had disappeared. In short, during the next day, her condition, mental and motor, underwent slight improvement.

On the 24th, two days after the first operation, Mr. Horsley freely laid open the mastoid antrum, middle and external ear, where there was extensive disease. The roof of the tympanum was found to be necrosed, causing a communication between the cranial cavity and the middle ear. The pus was very foul.

On the 25th, the patient's condition was generally improved, and the temperature in the rectum was not above 100° F.

The next day (26th), however, the patient became much worse, with increased paralysis. The wound was so foul that on the 27th Mr. Horsley again trephined behind the first opening. The dura mater and cortex were cut through to reach the abscess, which was freely opened backward.

The abscess was therefore now freely drained in every direction.

The following day (28th) the temperature reached 105° F. in the rectum, the patient never rallied, and she died on the morning of the 30th.

Just before death the temperature was 106° F. in the rectum.

The starting-point of the cerebral mischief in this case was, without doubt, an otitis media, as the second operation on the mastoid antrum and middle ear proved.

The post-mortem showed clearly how the infection had spread into the brain.

In the roof of the tympanum was a clean-punched-out hole in the petrous bone; over this the dura mater was wanting, but adherent around. There was, however, no sign of any meningitis.

The hole communicated with an extensive abscess burrowing under the cortex of the temporo-sphenoidal lobe.

The abscess was marked by a border, 5 or 6 mm. in thickness, of solid œdematous tissue.

The cerebellum, pons, and medulla were normal. There was no clot in the longitudinal sinus.

The right superior temporo-sphenoidal gyrus was partly undermined by the abscess, which extended to opposite the foot of the ascending parietal convolution.

There was nothing abnormal in the other organs, and there were no secondary abscesses.

From the history of the case, and the peculiar nature of the abscess wall, it was considered advisable to investigate the bacteriology, with a view to ascertaining the cause of the disease.

Bacteriological Investigation.

On December 1st, portions of the abscess wall were placed under the skin of the flanks of three guinea-pigs. The wounds were closed by suture, and dressed with collodion and wood-wool.

From other portions of the abscess, inoculations on sterilised potatoes were made.

Two days (December 3rd) later, two of the inoculated guinea-pigs began to show at the wound a little brawny nodule, which steadily increased in size.

On December 6th one guinea-pig was killed, as it seemed to be dying. At the seat of inoculation was a brawny swelling with a sunken dry scab, from beneath which a little thin pus exuded. On laying this open a well-marked cavity, containing some pus, was found. On section, the wall of the abscess cavity was 3 to 4 mm. thick, consisting from within out of a layer 1 to 2 mm. of thick purulent phlegmon, and outside this a zone of 1 mm. of congestion and hard œdema, whilst beyond was a variable amount of less dense œdema, which could be traced into the tissues for a distance of 1 cm. from the point of inoculation.

The glands in the neigbouring groin and in the abdomen were normal. There were no visceral lesions.

Microscopic examination of the abscess wall showed the following points :—

1. A necrotic zone consisting of débris, pus cells, and a variety of micro-organisms, amongst which cocci predominated. This passed into

2. A zone of leucocytic invasion and inflammatory exudation, and

3. A muscular layer, the fibres of which were in many places degenerating, and exhibited a pink reaction with the gentian violet, or stained deeply with carmine. The connective tissue between the bundles was very œdematous. The nuclei of the muscle fibres were exhibiting considerable activity. Between the fibre bundles, generally, and in some cases actually among the muscle fibres themselves, were scattered, somewhat sparsely, encapsuled diplococci. These were in lymphatic spaces, and did not appear to exist in the blood-vessels.

The capsules of the diplococci were distinguishable from the surrounding tissue by being particularly translucent. They were unstained, but the cocci were deeply stained by Gram's method.

A section of the abscess wall of the original brain showed similar encapsuled diplococci, situated remotely from the necrotic area.

From the abscess wall in the guinea-pig, gelatine, potato, and broth cultivations were made.

The fellow guinea-pig died on the following day (December 7th). At the seat of inoculation was an abscess very similar to that previously described. The peritoneum was rather œdematous; the inflammation had evidently spread along the urachus. The spleen was not enlarged.

As the third guinea-pig did not die, it was re-inoculated, but the reaction which ensued was only slight.

Two other guinea-pigs, inoculated from pieces of the abscess wall of the first animal, showed a marked brawny nodule at the seat of inoculation, were very ill, but eventually recovered.

A fifth guinea-pig, however, inoculated from the abscess wall of the second animal on December 7th, died on the 15th. There was the thick abscess wall, but the cavity contained nearly dry caseous material. A guinea-pig inoculated from this one recovered. Microscopically the walls of the above abscesses all presented practically the same appear-

ances as those described as occurring in the first animal. The chief feature was the presence of the encapsuled diplococci in the œdematous zone, while here and there nearer the abscess were longish rods and hyphal forms. In one or two places long rod-forms were found, in which segregation of the protoplasm had occurred, producing a beaded appearance.

Three out of the six animals recovered. (*Vide Table of Experiments*, p. 313.)

To return to the tube inoculations from the original brain abscess. These were made both on potato and on gelatine, with pieces of the abscess wall. The gelatine was quickly liquefied, and stank most offensively.

On the potato grew a variety of colonies, amongst which was a large brownish or buff-coloured mass. These colonies were subsequently isolated as far as possible on gelatine and potato.

Amongst those which liquefied the gelatine were a yellow form,—a staphylococcus,—several putrescent varieties, and a bacterium which produced a beautiful greenish fluorescence on the gelatine. None of these, however, microscopically, were at all like the diplococci forms described above in the abscess wall.

The large buff colony was inoculated afresh on potato, agar, and gelatine, and after repeated attempts was obtained apparently pure. On different potato cultivations the microscopical results showed an apparent discrepancy. For in some instances there were many diplococci forms, mixed with, perhaps, only a few threadlike and bacterial forms, whilst in one preparation I obtained only the thread-like variety. Occasionally a few hyphal forms were met with. In addition I often found individuals staining, in some cases, more deeply, in others less deeply, than the majority in the preparation.

The explanation of the varieties in form is derived from facts ascertained at a later stage; but the reason of the variations in staining I have, as yet, been unable to discover. The fact, however, that in the case of the cocci one member was stained deeply and the other lightly, suggests that the protoplasm of the latter was becoming devitalised.

A similar buff colony was obtained from tubes inoculated with the abscess walls of the guinea-pigs. These contained several forms, amongst which were diplococci and rods, like those seen in the abscess walls. None were encapsuled. It is, however, well known that in all artificial cultures such organisms lose their capsules.

So far guinea-pigs had been inoculated with pieces of the abscess wall only, and therefore had necessarily been infected with a mixture of micro-organisms.

It was, however, now not improbable that the lesion was due to a diplococcus, since it had been found in every abscess wall, and in the cultivations made from those abscess walls.

Assuming this to be the buff colony, which now seemed to be in a

pure state of cultivation, I injected a broth culture of it under the skin of a seventh guinea-pig.

Microscopically this broth culture is extremely interesting, for although obtained from an apparently absolutely pure culture, it contained a variety of forms ranging from diplococci to oval rods in pairs (Figs. 3 and 5), and from these to long rods. What was the meaning of this? Was this a micro-organism exceptionally pleomorphic, or

From Micro-Photographs by the Author.

FIG. 1.—Pink rod form.

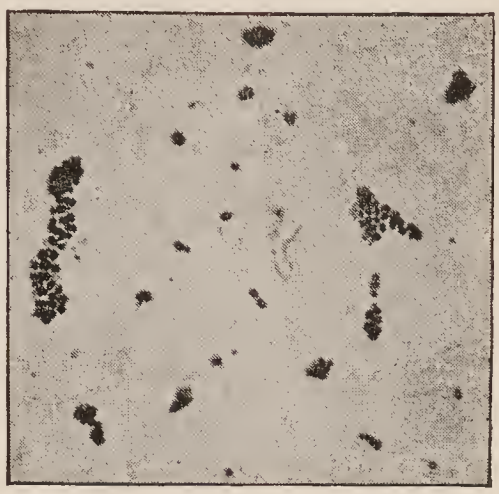

FIG. 2.—Buff coccus form.

FIG. 3.—Buff bacilli.

FIG. 4.—Pink rod form.

FIG. 5.—Buff form from œdema fluid.

had I a mixture of several organisms nearly related but differing slightly morphologically? On a potato inoculated with this broth culture appeared a thin buff colony, with a slight tendency to spread.

The guinea-pig which had been inoculated with 1 c.c. of the broth culture died within 36 hours. From outside no thickened œdematous tissue in the neighbourhood of the puncture was to be felt. On the right flank, however, at the point of injection, a large area of skin, 3 in. × 2 in., was raised and separated from the chest wall beneath by œdema

fluid. There was no pus. There was nothing abnormal in the peritoneum, save some quite recent peritonitis. The heart was engorged on the right side.

Microscopical examination of the œdema fluid proved it to be swarming with a number of very large broad rods with rounded ends, mostly in pairs: large diplococci, out of which the long rods seemed to have developed (Fig. 3). Here and there were smaller diplococci: in one place, these were arranged chain-wise. The protoplasm in the larger rod, as seen under Zeiss $\frac{1}{12}$ oil immersion, with 18 compensation ocular, was segregated in some, homogeneous in others; and, where the segregation had apparently gone far, only a sort of husk was left, stained faintly, after Gram's method (Fig. 6).

Neither before nor since have I been able to reproduce this intense œdema in a guinea-pig—an œdema comparable to that of anthrax in rabbits. Nor have I again been able to cultivate the buff colony obtained from this fluid on potato, to such a size as it appeared in this case. Œdematous tissue has been produced in subsequent guinea-pigs, but the organisms have always been the size originally obtained.

From this œdema fluid cultures were made on potato, agar, and gelatine. On the potato a buff colony appeared, similar to what I had obtained before. The gelatine was not liquefied, but both on that and on the agar white colonies grew, which were homogeneous, and which tended to spread over the whole surface. On the agar especially there was a tendency to an in-dipping of the growth.

It seemed, therefore, on December 21st, that at length I had succeeded, in obtaining a perfectly pure culture, in injecting it into an animal, causing its death, and in cultivating the organism pure again from the animal; further, that this organism tallied in some forms with what had been seen in the tissues, there seemed to be no doubt.

I was not able to resume work again until January 4th, 1892. I then found that on all my potato cultivations of the buff colony, including those earlier ones obtained from the brain itself, there appeared, dotted along on the buff, a delicate rose-tinted growth. Thus this pink growth not only came from the original brain cultures, but also appeared on those cultures made from animals which had been inoculated with brain substance.

The question then arising as to which was the pathogenic micro-organism, the two forms, the buff and the pink, were separated.

To return to this mixed cultivation. While admixture was plain on potato, there was no evidence of such on either agar or gelatine. Did the pink colony then not grow on these two media, or had it an identical growth with the buff? The latter was found to be the case; and, unless the growth was of some duration, no pink coloration ever showed at all.

Microscopically the similarity between the two organisms is very great: the differences are tabulated below.

Inoculation with the separated buff colony produced in guinea-pigs an œdematous infiltration at the seat of puncture. Diplococci were found deep amongst the muscle fibres, whilst short-rod shaped forms also occurred.

The inoculation of an animal with the pink colony produced little or no effect, and no diplococci occurred far away from the centre of inoculation, as in the case of the buff. Numerous diplococci, sporulated rods and hyphal forms occurred in one animal, but nothing was found in another. I consider this organism non-pathogenic.

Two further confirmatory experiments were made with regard to the buff colony.

The conclusion I draw is that this buff organism produces a primary lesion causing œdema and degeneration of the affected part, but does not necessarily lead to the formation of a typical abscess.

I believe it was the primary cause of the disease in the case cited at the beginning of this paper.

FIG. 6.—The buff colony from œdema fluid.
Zeiss $\frac{1}{12}$ Obj. Oc. 18 Comp. ×2500.

FIG. 7.—The pink colony from culture.
Zeiss $\frac{1}{12}$ Obj. Oc. 18 Comp. ×2500.

MORPHOLOGY.

The Buff or Pathogenic Organism.

This micro-organism consists for the most part of fair-sized diplococci, which in the animal exudate, blood and tissues, are encapsuled. In artificial cultures the capsule is lost. The cocci are from 1 μ to ·75 μ in diameter.

Besides, however, the diplococci forms, paired rods with oval ends are found, both in the tissues and artificially. Between these are intermediary growths, so that there is a complete series from cocci to bacilli. It appears further that each coccus may, when growing very rapidly, divide at right angles to the axis of the pair, producing half-moon forms. This may throw some light on the formation of the tetrad, unless one considers that to be a twin diplococcus.

The actual size of the various forms is by no means constant. They vary from 4 μ to 6 μ in length, and are 1 μ in breadth. In some places the rods are clavate in form: this suggests that the formation of such a rod with a constricted centre is a step towards the diplococcus form, Paired dots and elongating pairs have been found in the tissues embedded in a single capsule. This is not, however, usual. The nature of the growths on various nutrient media is as follows:—

The organism grows on potato, agar, gelatine, and in broth.

Potato.—It grows rather slowly at 16° C. in softish moist dotted colonies, which later coalesce, forming a thinnish layer on the potato. The colour is somewhat buff, but after repeated cultivation tends to fade, until a cream-coloured culture is obtained. The surface, though rather moist, is rough and irregular. The growth is never extensive or thick.

Agar.—It grows in a thin layer, with a tendency to spread. The thickness of the growth is unequal, and the surface uneven, though tending to be moist. The colour is cream in the less transparent portions of the growth. Occasionally, at certain points, there is a tendency to an indipping of the growth.

Gelatine.—It does not liquefy. Same appearance as on agar. The edge of the colony under a low power is seen to be irregularly rounded and fissured. The growth seems to proceed radially from many points in the same neighbourhood, and hence the rounded and lobed appearance, not unlike a thick section of pancreas. The naked-eye irregularities on the surface are evidently due to this mode of growth. Under the microscope there is, in the thicker portions, a brownish tinge.

Broth.—There is some clouding, and a white sandy deposit is seen after 24 hours, at a temperature of 34° C.

The Pink or Non-Pathogenic Organism.

This organism is remarkable for its pleomorphism. Microscopically, it is impossible to distinguish the diplococcus form from that of the buff. The rods, however, as is shown by the photographs (Figs. 6 and 7), are much thinner and longer. They measure from 4 μ to 12 μ in length, and are about ·5 μ in breadth. They do not seem to stain quite so deeply when Gram's method is used. But besides the bacilli, leptothrix forms occur, the threads being often in pairs. So here we find a complete series from the diplococcus to the paired rods, and thence to long threads, singly or in pairs. In some of the rod-like forms a segregation of the protoplasm is observed. The arrangement is such that each member of a pair stands beside its fellow, in an axis at right angles to the axis of the thread, so that we do not have a true chain of diplococci all lying in the same axis, as in Fränkel's [1] organism, but possibly a mode of spore formation.

[1] Pfeiffer and Fränkel's "Atlas," 1891.

The following are the characteristics of the cultures:—

The organism grows on potato, agar, gelatine, and in broth.

Potato.—It grows rapidly at 16° C., tending to spread over the surface of the potato, and to become heaped up into a thick mass. The colour is a delicate pink. The surface is smooth and moist, sloping convexly toward the edge of the growth. When the tube is capped, so that exchange of air and evaporation cannot take place, the colony tends to lose its pink colour, especially towards the growing edge. If allowed to dry, the colour becomes darker and less transparent-looking, and the surface roughly granular. The growing edge is fairly regular.

Gelatine.—It does not liquefy. The growth is opaque, smooth and moist on the surface. It tends to spread over the surface, proceeding in irregularly-rounded clumps; is, when young, of a cream colour, but when old and allowed to dry it becomes distinctly pinkish in tinge. It does not grow so luxuriantly as on potato. Microscopically the growing edge is remarkable, especially in a tube in which slight evaporation has been allowed to go on. It is made up of numberless spikes which centrally are united into a solid mass, but peripherally the growth is irregularly branched. Under a higher power ("C." Zeiss) it is seen that the branches are also made up of these processes, which in their turn form branchlets. To the naked eye, a feathery outline occurs round the more solid part of the growth.

Agar.—Similar to gelatine. The branching, however, is not so well shown.

Broth.—Becomes cloudy; there is a granular deposit at the bottom, and a tendency to rod and leptothrix formation.

I must here acknowledge my thanks to Professor Carl Fränkel of Marburg, to whom specimens and tubes were sent. He considers that both these micro-organisms are morphologically allied, and finds they are new to him. He confirms the observations as regards the variations in form, and with the buff has produced subcutaneous abscess.

He draws attention to the similarity, morphologically and biologically, both have to bacterium coli commune, but considers that they are entirely distinct.

He states that Schimmelbusch[1] has recorded certain cases of noma in which a bacillus, which has many points in common with those found in this case, occurred.

This research was undertaken at the suggestion of Professor Horsley, who was struck by the noma-like appearance of the abscess. I am deeply indebted both to him and to Professor Boyce for their help and advice.

My thanks are also due to the examiners for the Liston Medal for their permission to publish this paper.

[1] *Deutsche med. Woch.*, 1889, p. 26.

COMPARATIVE TABLE, SHOWING DIFFERENCES BETWEEN ABOVE ALLIED ORGANISMS.

	Buff Colony.[1]	Pink Colony.[1]	Fränkel's Pneumo-diplococcus.	Friedländer's Pneumo-bacillus.
Microscopic characteristics.	A diplococcus encapsuled, growing into paired rods and chains of rods. Encapsuled in tissues. Rods are from 4 μ to 6 μ long, and 1 μ broad.	A diplococcus lengthening into rods, and ultimately into leptothrix forms. Encapsuled in tissues. Rods are from 4 μ to 12 μ in length, and ·75 μ broad.	Occurs in single pairs, and pairs in chains. Encapsuled in tissues.	Has a tendency to assume rod forms with oval ends. *Vide* Fränkel's "Atlas," 1892. Encapsuled in tissues.
Staining reactions.	Well with Gram, and other nuclear stains.	Well with Gram, and other nuclear stains.	Stains with Gram.	Decolorised by Gram.
Growth on potato.	Brownish colony, does not grow fast.	Pink colony, grows rapidly, with a tendency to heaping up.	Does not grow.	White yellow, moist, glazed, stretching over whole surface. Forms gas bubbles at incubating temperature.
Growth on gelatine.	White, tendency to dipping down into the substance; grows at ordinary temperature, slowly.	White, later pinkish, tendency to spread rather than dip, grows at ordinary temperature.	Will not grow under 20° C.; best at 35°–37° C.	In twenty-four hours porcelain white points. Gelatine not liquefied. Gas bubbles; old cultures, light yellow brown.
Growth on agar.	Similar to gelatine.	Similar to gelatine.	Homogeneous; does not dip into the agar.	Similar to gelatine.
Broth.	Tendency to short thick rod formation. Granular precipitate.	Tendency to slender rod formation. Granular precipitate.		
Pathology, etc.	Causes a spreading œdema found generally as encapsuled diplococcus, somewhat remote from necrotic area of the abscess wall. Virulence diminished by repeated cultures on potatoes, as well as rapidity of growth.	Non-pathogenic, found in the more necrotic part of the abscess wall.	Has been found in numerous cases of pneumonia, and in otitis media, and epidemic cerebro-spinal meningitis. Artificially inoculated, produces an intense spreading œdema (Foa and Bordoni Uffreduzzi). Not found in white corpuscles. (?) Immunity afforded by one injection. Virulence and vitality soon lost in artificial cultures.	Reputed cause of certain cases of pneumonia. Occasionally found in otitis media.

[1] For more minute details, *vide* pp. 309 and 310.

TABLE OF EXPERIMENTS ON GUINEA-PIGS.

Animal.	Source of Inoculation.	Nature of Lesion.	Duration of Life.
Guinea-pig 1.	Original abscess wall from brain.	Brawny nodule on third day, which increased in size. Post-mortem—Abscess cavity, with thick wall containing cheesy pus, with some fluid.	Five days. Killed while dying.
Guinea-pig 2.	Original abscess wall from brain.	Similar.	Six days.
Guinea-pig 3.	Abscess wall of guinea-pig 1.	Brawny nodule; animal became decidedly ill.	Recovered.
Guinea-pig 4.	Do.	Do.	Do.
Guinea-pig 5.	Abscess wall of guinea-pig 2.	Brawny nodule, containing nearly dry caseous pus.	Seven days.
Guinea-pig 6.	Abscess wall of guinea-pig 5.	Brawny nodule.	Recovered.
Guinea-pig 7.	Apparently pure culture (broth) of buff from original brain. 1 c.c. injected.	No nodule; but subcutaneous œdema fluid, containing large paired rods.	Thirty-six hours.
Guinea-pig 8.	Pure buff colony from potatoes, inoculated with œdema fluid.	Wound became infected accidentally. Nodule and abscess cavity. Abscess wall contained diplococci far in tissue.	Killed.
Guinea-pig 9.	Pure pink colony from above potato (having appeared in dots on the buff).	Wound accidentally infected. Causing abscess: no diplococci deep in the tissues, but only at margin of abscess, together with long hyphal rods.	Killed.
Guinea-pigs 10 and 11.	Injection of pure cultivation (broth) of buff.	Local œdema, and thickening of the tissues at seat of inoculation.	Recovered.
Guinea-pigs 12 and 13.	Injection of pure cultivation (broth) of pink.	No result.	Recovered.

LITERATURE AND BIBLIOGRAPHY.

From investigation of the literature on the bacteriology of otitis media purulenta I find that about half the cases recorded have been due to pyogenic micro-organisms, strepto- and staphylococci;—citreus, aureus, etc.

In the remaining half, with the exception of two cases, Fränkel's pneumococcus has been cited to be the cause, though generally there has been secondary infection with staphylo- and streptococci (Netter, Zaufal, Moos).

In two cases only was Friedländer's pneumo-bacillus found to be the

cause. These were recorded by E. Zaufal[1] and Weichselbaum.[2] In this last case there was, to begin with, an acute rhinitis.

Bordoni-Uffreduzzi and Gradenigo[3] summarise incompletely, and give the results of their own observations.

They found in the secretion lancet-formed diplococci,—some in cells, others free. In one case, after 15 days of acute otitis media, they found chains of diplococci (as many as 14 pairs together) in a clear capsule. These stained well with Gram. These diplococci produced no effect upon rabbits, but mice died in 4 days. There was a little œdema at the seat of infection, and the blood contained many encapsuled diplococci. On gelatine the growth was slow, consisting of small round colonies along the stroke. On agar the culture spread over the whole surface in a fluid manner at 37° C.

It is commonly stated that in children the majority of middle ear lesions are tubercular; how far this is so I am unable to say; but this would appear from continental writers to be by no means always the case.

Influenza is not an uncommon antecedent of otitis media (*vide* Bibliography). In the case above described there is a very good history of some such affection. It would seem most probable that, when there is no wound of the tympanic membrane, the infection has spread up the Eustachian tube. We have very strong evidence in favour of the direction of infection in the fact that the diplococcus pneumoniæ of Fränkel and Weichselbaum is found in 50 per cent. of the cases of otitis media. Further, in connection with cerebral lesions, it is acknowledged that in several epidemics of cerebro-spinal meningitis of children, this same micro-organism has been recognised as the cause.

The Bacteriology of Otitis Media.

Bordoni-Uffreduzzi and Gradenigo.	A new strepto-diplococcus. Bacteriology of 33 cases of otitis media; Fränkel's pneumococcus in 16. *Centralbl. f. Bakteriologie*, 1890, Bd. vii.
Levy, ...	*Centralbl. f. Bakteriologie*, 1890, Bd. viii., p. 87.
Moos, ...	*Centralbl. f. Bakteriologie*, 1888, Bd. iv.
Netter, ...	Recherches bact. sur les otites moyennes, etc. *Annales des mal. de l'oreille* 1888; *Centralbl. f. Bakteriologie*, Bd. vi., 1889, p. 615. Le Pneumococque, *Arch. de méd. exp. et d'anat. path.*, 1891.
Rohrer, ...	Cocci and clostridium butyricum. *Centralbl. f. Bakteriologie*, 1888, Bd. iii., p. 644.
Story, ...	Aspergillus niger. *Ibid.*, p. 177.
Zaufal, ...	Der eiterbild. Kettenkokkus bei Otitis media, *Prag. med. Woch.*, 1888, Nos. 21, 22. Fränkel's diplococcus, 4 cases, mastoid abscess, *Centralbl. f. Bakteriologie*, 1889, Bd. vi., p. 508; *Ibid.*, 1887, Bd. ii., p. 560; in acute case, Friedländer's pneumo-bacillus; in acute case, Fränkel's pneumococcus.

[1] *Centralbl. f. Bakteriologie*, 1887, Bd. ii., p. 560.
[2] *Ibid.*, 1889, Bd. v., p. 423. [3] *Ibid.*, 1890, Bd. vii.

Influenza a Cause of Otitis Media.

Habermann, ... Zur Erkrankung der Ohren bei Influenza, *Prag. med. Woch.*, 1890, No. 8. 39 cases, 18 of which were cases of otitis media simplex. In 21 the tympanum was perforated.

Rohrer, F., ... Erkrankung des Ohres bei Influenza, *Archiv f. Ohrenheilkunde*, 1890, Bd. xxx., p. 119. 61 cases, 18 of which had purulent otitis media and 22 catarrhal.

Jansen, A., ... Influenza-Otitis, *Archiv f. Ohrenheilkunde*, 1891, Bd. xxxi., p. 155. Enormous increase of otitis media in the Berlin Klinik during influenza epidemic.

Hessler, ... Ueber Otitis bei Influenza, *Archiv f. Ohrenheilkunde*, 1891, Bd. xxxii., p. 29. 12 cases operated on, by free opening of antrum; one death; the rest healed, generally in 3 weeks.

Ludwig, Politzer, Dreyfuss, Lowenberg, and others, quote cases of otitis media following influenza.

In the Ear Department of University College Hospital, Mr. Pollard noticed that during the epidemic of influenza, 1890–91, the purulent otitis media was far more frequent than it has been during the present one, 1891–92.

Otitis Media and Cerebral Abscess.

Gruber, ... Diseases of the Ear, 1890; translation by Law and Jewell, pp. 371, 378, 380.

Paths of cerebral infection, etc. are: (1) apertura spuria canalis Fallopii; (2) intern. aud. meatus; (3) aqueducts of vestibule and cochlea; (4) petro-mastoid canal; (5) extension to lateral sinus with thrombosis and phlebitis.

Körner, Otto, ... Zur Kenntniss der bei Felsenbeincaries auftretenden letalen intracraniellen Erkrankungen, *Archiv f. Ohrenheilkunde*, 1889, Bd. ii., p. 126. (Hirnabscess, etc.) 67 cases of abscess; cerebral, 31; cerebellar, 19; remainder mixed. 61 cases of thrombosis of lateral sinus, complicated.

Barr, ... Address on Cerebral Abscess from Middle Ear Disease. Fifty-sixth annual meeting of British Medical Association.

Mourc of Bordeaux records a case of Cerebellar Abscess, with Sinus Thrombosis (1889).

Lannois, of Lyons, . . . 2 similar cases.

Boke, Julius, Buda Pesth, Ein besonders interessantes Fall von Abscessbildung über dem Processus Mastoideus, *Archiv f. Ohrenheilkunde*, Bd. xxvii., p. 90. Otorrhœa, 16 years; meningeal symptoms; mastoid abscess drained. 14 days later, pharyngeal abscess burst spontaneously. Ein Fall von Gehirnabscess und Cholesteatum in der Paukenhöhle, *Jahrbuch der Gesell. d. Ærzte in Buda Pesth*, 1889, pp. 97–99. Patient, æt. 16, otitis media; perforation of roof of tympanum; abscess in temporo-sphenoidal lobe; basal meningitis; death; no operation.

FRIEDENWALD, ... Meningitis; thrombosis of lateral sinus; death; *Archives of Otology*, New York, 1891, vol. xxi., p. 1.

DOWD, C., ... Abscess of temporo-sphenoidal lobe after otitis media; *Medical Record*, New York, 1891, vol. xxxix., p. 183. Scarlet fever; chronic otitis; the cerebral motor symptoms not marked; abscess, size of hen's egg, with infiltrated walls; petrous portion of temporal bone destroyed.

SIMON, EMIL, ... Beitrag zur Casuistik abscederender Hirnentzündungen nach Otitis media purulenta chronica Greifswald, 1890.

HOFFMANN, ... Zur Pathologie u. Therapie der Pachymeningitis externa purul. nach Entzündungen des Mittelohres, *Deut. Zeit. f. Chir.*, Bd. xxviii., Hft. 4 and 5.

BACON, GORHAM, ... Chronic otitis media; perforation; small temporo-sphenoidal abscess; death from secondary hæmorrhage; *Archiv f. Ohrenheilkunde*, 1889, Bd. xxviii., p. 91.

GRADENIGO, ... Ueber die Classification u. Ætiologie der mittelohr Entzündungen in Allgemeinen, *Allg. Wien. med. Zeit.*, 1891, Bd. xxxvi., p. 331.

MILLIGAN, ... Chronic Suppuration of Middle Ear; analysis of 300 cases; *Med. Chron.*, Manchester, 1891, vol. xiv., pp. 409–412.

CEREBRAL ABSCESS, ETC., FOLLOWING OTITIS MEDIA. CASES OPERATED UPON.

BARR, THOMAS, Glasgow, . Fall von durch Ohrerkrankung bedingtem Hirnabscesse, in welchem von Dr. W. Macewen, der Schädel trepanirt, ein Abscess im Temporo-Frontallappen gefunden und entleert wurde; vollkomenne Heilung. *Zeitschr. f. Ohrenheilkunde*, 1888, Bd. xviii., p. 72.

Patient, schoolboy, æt. 9. Pain in affected ear 3 months; offensive otorrhœa; perforation of tympanum, through which the pus welled out. *Symptoms*—repeated rigors, pains now gone, somnolence, prostration, foul smelling expectoration; ptosis, right eye; right face slightly paralysed; pulse, long, weak, and intermittent. Operation by Macewen through squamous portion of the temporal bone; congested dura cut through; brain explored with a needle—foul gas and pus. Counter opening at base of temporal bone; washed out with *boracic*, drainage tubes of hen's bones. Complete recovery; a dry perforation of tympanic membrane.

BARKER, ARTHUR, . . . Ein Fall von Meningitis in folge von Otitis media. *Wiener med. Blätter*, 1888, No. 25. Boy, æt. 7; post-scarlatinal, otitis media purulenta; trephined; cured.

BRAUN, EDUARD, ... Die Erfolge der Trepanation bei dem otitischen Hirnabscess, *Archiv f. Ohrenheilkunde*, 1890, Bd. xxix., p. 161.

An interesting article, quoting cases up to date; cases of the author's, with his theories on the patho-

logy and treatment. He gives a detailed comparative analysis on the treatment after trephining, relative to healing, of the cases under Macewen, Greenfield, Barker, Horsley, Gussenbauer, and Bergmann.

STATISTICS.[1]

1. Schede, 1885,		Von Bergmann's Collection, 1889.
*1. Von Bergmann, 1888,		
*1. 2. Barker,	1886–88	
*1. 2. Macewen,		
*1. Horsley,		
*1. Greenfield,		

* Recovered.

CHIPAULT, ... *Bulletin Soc. anat. de Paris*, 1888, p. 856. Unsuccessful case of trephining; the abscess proved to be cerebellar; the patient 3 months before death had become suddenly deaf; he died $2\frac{1}{2}$ months after appearance of first (other) symptoms.

ORLOW, ... Ueber Trepanation des Schläfenbeins bei Thrombose des Sinus transv., *Deutsche med. Woch.*, 1889, No. 10. Purulent otitis for 3 weeks; abscess cleared out between dura and the bone.

SAHLI, HERMAN, ... Ueber hirnchirurgische Operationen vom Standpunkte der inneren Medicin, *Sammlung klinischer Vorträge*, Volkmann, Neue Folge, 1891, No. 28, pp. 13, 14, 18.

PAGE, H. W., ... Two cases of middle ear disease; operation for relief of cerebral complications; *Lancet*, 1891, vol. ii., p. 231.

SCHMIEDT, Metz, ... Hirnabscesse nach geheilter Otitis media purulenta acuta, *Archiv f. klin. Chir.*, Bd. xxxviii., p. 790.

Acute otitis media, healed in 4 weeks; patient died later; at post-mortem no pus in middle ear, though there was a large abscess in the temporo-sphenoidal lobe; the temporal bone was intact.

BARKER, A. E., ... Hunterian Lectures, 1887; Address to Glasgow Medico-Chir. Soc., *British Medical Journal*, 1886, vol. ii., p. 1154; 1887, vol. i., pp. 407 and 538.

PICQUÉ, ... Abcès cérébral consécutif à une otite moyenne suppurée, *Annales des maladies de l'oreille, du larynx, du nez, etc.*, 1890, tome xvi., p. 437.

Patient, æt. 46. Dec. 1889, Influenza, and suppuration of right middle ear. April 16, 1890, Hemicrania, severe. April 17, Temperature, 39°·5 C.; complete left-sided hemiplegia. April 18, Mastoid opened; no pus. Trephined over motor area; after incision of dura mater, brain bulged abnormally; abscess opened and drained. Symptoms relieved until April 24, when temperature went up 40° C.; patient sank in coma. Post-mortem—general encephalitis, and a smaller unopened abscess.

FAGGE AND PYE SMITH, . Principles and Practice of Medicine, 1891, p. 632. Give statistics which differ from von Bergmann's, and are more complete.

[1] These are not exhaustive.

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MADURA FOOT OF INDIA.

By N. F. SURVEYOR, M.D.

From the Pathological Laboratory of University College, London.

THE fungus-foot disease of India is always a very chronic affection, and it has never been found to become generalised. It is purely a local disease of the extremities, chiefly the foot. It generally occurs in people who go barefooted and are working in fields. In most cases it has been traced to some injury. The big toe is often affected first. The disease stops at the ankle for a short time, then it spreads up to the knee, and may go up to the thigh too.

Clinical Appearances.—In the full developed state the whole foot swells up to about twice its original size; the skin becomes thickened and pigmented; the toes appear retracted, and the patient limps about on the heel for some time till he cannot bear the pain, but finally drags himself in the sitting posture. The foot looks like a foot in scrofulous disease of the tarsal bones. It is covered over with sinuses, which go deep down in the tissues, and the openings are surrounded by raised margins. From these openings a purulent and sanious discharge can be pressed out, and in it are small particles which are about the size of millet seeds, and are tuberculated. These may be red, black, or yellowish-white in colour, but never like the sulphur-coloured bodies found in actinomycosis. If the disease is of recent date, nodular bodies are found which vary in size from a pea to a small marble. On cutting these open in the centre small particles like those already

described are found. The disease is very chronic ; it may last for twenty-five years.

Course of the Disease.—One peculiarity about this disease is the absence of any active constitutional symptoms. Slight hectic and emaciation occur only when the disease has lasted for some years. It begins as a nodule on the foot, which becomes slightly painful and ultimately bursts, leaving a sinus, which does not heal, and from which the particles can be pressed out. Other nodules are found there, and the resulting sinuses are found to communicate with one another. The tissues around the sinuses get thickened, the muscles atrophy and show fatty degeneration, while the bone gets softened and porous.

Microscopical Appearances.—I have examined sections showing the white variety only, and these show fibrous capsules in which peculiar homogeneous reniform bodies can be detected. The periphery of these bodies shows small bodies, which may be clavate or not. Radiating from the periphery are long gelatinous filaments, and the free ends of these are covered over with granular cells. Dr. Carter, in his classical work on this subject, gives the diagram of a round body covered over with similar filaments. These he looks upon as fatty crystals. Drs. Lewis and Cunningham, in their paper on the subject, described similar filaments, and agree with Dr. Carter in calling them fatty crystals. All my specimens, having been soaked for about three days on an average in ether and then in ethereal solution of paraffin, would not have shown these filaments if they had been simple fatty crystals. Besides that, the paraffin was always dissolved out of the sections before staining them by means of ether. The sections were fixed on cover-glasses with Mayer's albumen.

Various stains were used to get the best staining reaction. Of these, the following have been chiefly used : Boström (not very successful), S-fuchsine,Hoffmann's blue, gentian-violet after Gram's method, picro-lithium, carmine, borax, methylene-blue (Sahli), safranin, hæmatoxylin, and Biondi's stain. The great difficulty in staining was to stain in such a way as to make the filaments take up enough colour without over-staining, and thus obscuring the appearance of the reniform bodies. The homogeneous reniform bodies, for instance, took up the Sahli blue very easily, while the filaments remained colourless. To stain the latter I used alcoholic solution of eosin, which decolorised the whole

specimen except the homogeneous reniform bodies, and at the same time stained the filaments red. The great objection to Sahli's method is that the stain is often not permanent. An experiment with Sahli, counterstained with picric acid, and clarified in a mixture of equal parts of xylol and oil of cloves, was tried. The great difficulty in this was to get rid of fine acicular blue crystals, which are precipitated on the specimen, especially near the reniform bodies. Here the filaments become greenish-yellow, and the central part blue. The reniform bodies take up hæmatoxylin very easily, and make them almost opaque if left too long in the stain. Counterstaining with eosin stained the filaments and clubs. Safranin is a very pale and delicate stain, which does not bring out the details of the filaments very clearly, but shows the reniform bodies very well. Picrolith-carmine stains the reniform bodies of a pale pink colour, while the clubs take up the carmine deeply. The filaments take up the picric acid. The best stain was gentian violet, used after Gram's method. The sections must be left in the gentian-violet (Weigert's formula) solution for about ten minutes; then they are to be washed with water, and put in Gram's iodine solution. In Gram they are to be left for about three to five minutes; rinse again in water, and finally transfer to spirit. They are not to be allowed to lose the gentian violet to any great extent in the spirit, as a good deal is sure to come off in the oil of cloves. This method stains the filaments of a pale blue; the reniform bodies are violet, and the clubs are deep blue. Biondi's stain makes the filaments and the clubs red, while the reniform bodies are blue. Here the dehydrating must be rapidly done, as the blue is extracted in the process.

In some cases I found small round bodies which took up a violet colour when either gentian-violet or Biondi was used. These were either single or sometimes in small clusters, and sometimes two such bodies were seen encapsuled together. Again, in one place I saw a very small fan-like body with short finger-like processes. The whole body was surrounded by a homogeneous gelatinous substance. A short time before leaving India, Dr. Carter recorded two cases in which the fungus resembled the actinomyces fungus. However, he was careful to state that that was the case in those two specimens only.

Differences between Madura Foot and Actinomycosis.—To

sum up some of the chief points in which the disease differs from actinomycosis hominis. (*a*) Madura foot is invariably a chronic disease. (*b*) The internal organs are never affected as far as our present knowledge goes. (*c*) The constitutional symptoms are always very slight. (*d*) Actinomycosis hominis is almost unknown or very rare in India. (*e*) The sulphur-coloured bodies of actinomycosis hominis have never been detected. (*f*) The peculiar homogeneous reniform bodies with the clubs and filaments look at least like some ray-fungus.

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ENLARGEMENT OF THE HYPOPHYSIS CEREBRI IN MYXŒDEMA; WITH REMARKS UPON HYPERTROPHY OF THE HYPOPHYSIS, ASSOCIATED WITH CHANGES IN THE THYROID BODY.

By Rubert Boyce, M.B., M.R.C.S., *Assistant Professor of Pathology in University College, London*, and Cecil F. Beadles, M.R.C.S., L.R.C.P., *Assistant Medical Officer, Colney Hatch Asylum.*

(Plates XVIII. and XIX.)

From the Pathological Laboratory of University College, London.

The resemblance of the glandular tissue of the pituitary body to that of the thyroid has long been known. In 1866 Peremeschko[1] carefully described the hypophysis in the lower animals and in man, and contrasted its structure with that of the thyroid.[2] It was not, however, until 1886 that Rogowitsch[3] showed, by experiment, that a probable close relationship existed between these bodies. As will be seen later on, his results have been confirmed by several other observers. In the human subject but few observations have been made upon the condition of the hypophysis in disease of the thyroid. In like manner, although the records of the tumours and other diseased states of the hypophysis are very numerous, yet no special attention has, so far, been directed to the condition of the thyroid, or of the system generally, in these cases. In the future, no doubt, more attention will be paid to this subject, seeing that, recently, important functions have been ascribed to the hypophysis.[4]

The cases in which hypertrophy of the hypophysis, with absence or disease of the thyroid, have been recorded in man include probably two cases of sporadic cretinism in which the thyroid was absent, and one case of fibroid goitre. In acromegaly, as is well known, the enlargement of the pituitary is a striking feature, but, as will be seen further on, this change is sometimes associated with a hypertrophied, sometimes with

[1] Peremeschko, *Virchow's Archiv*, Band xxxviii., 1867.

[2] Previous observations on this subject appear to have been made by others, notably by Michel, *Charleston Med. Journal*, 1860.

[3] Rogowitsch, *Ziegler's Beiträge*, Band iv.

[4] Horsley, *Virchow's Festschrift*, 1891; and Gley, *Bulletin de la Soc. de Biologie*, 1891; and *Archives de Physiologie normale et pathologique*, April 1892.

an atrophied or otherwise diseased, thyroid. In the following pages we shall bring forward two cases of *myxœdema*, with atrophied thyroids and enlarged pituitaries, and one case of *sporadic cretinism* in which similar conditions obtained.

Case 1.—*Myxœdema.*

Lucy D——, æt. 42, was admitted into Colney Hatch Lunatic Asylum as insane, on the 19th January 1884.

She had been a domestic servant. This was her first attack, and was then of about seven days' duration, and she had not been under previous care or treatment. There was a suicidal tendency; she was not subject to epilepsy, nor was she dangerous to others. The cause was stated as not known.

The medical certificate upon which opinion of insanity was founded states: "Has slight wounds on her throat, which she tells me she did in attempting to destroy herself. Imagines persons have taken improper liberties with her, and that her husband is dead." "Her husband informs me that Lucy D—— attempted to cut her throat, and wanted to go out of the house partly dressed."

On the day of admission, patient is stated to be "in good bodily health and condition. Weight, 9 st. 4 lbs. Reads and writes. Deluded as to people following her," etc.

Delusions continued for a week or two, during which time patient was restless and confused. On February 15th following, she was discharged recovered, her weight being the same as that on admission.

On July 3rd, 1884, she was readmitted into Colney Hatch on a second medical certificate, running as follows:—"Imagines people are following her about, and that the Prince of Wales comes to see her, and sends her money, which the attendants destroy." "Sarah G——, her sister, informs me that Lucy D—— wanders about the streets at night, and was found by the police in an excited state, and unable to give an account of herself."

The present attack was said to be of ten days' duration. She was entered as a case of general paralysis, being deluded and of simple mind. Her weight was 9 stone.

July 10th.—Was certified to the Commissioners "That, as to her mental state, she is maniacal and deluded as to Royalty; ideas confused and restless. She is in fair bodily health and condition."

On December 10th following, there is said to be "No improvement mentally; very deluded and rambling in her statements; is stout, and has a high colour. Speech halting and unsteady."

A year later (August 12, 1885) she is "deluded and very incoherent; not violent nor suicidal, but restless and stubborn; stout and hearty, but too fat and florid."

February 8th, 1886.—Her mental condition being the same, it is said that "her body is well-nourished, but she has œdema of the feet and ankles, and puffiness about the eyelids. Speech slow and halting, and she has slight epileptiform attacks at intervals." In the following September there is an entry, "Is thought to be a case of myxœdema."

March 4th, 1887.—It is said that "the œdema rather increases"; and in November 1st, she was said to be in fair health, having "appeared to improve greatly under jaborandi."

From this time onwards the patient appears to have gradually got worse, but rallying and somewhat improving at times. She was better in the summer months. Several times in the colder weather she was thought to be dying.

In 1889 she was very feeble and weak, and towards the latter part of the year she was becoming demented. In February 1891 she had "well-marked myxœdema."

During the last few months of her life, the myxœdematous condition increased greatly, and she was extremely weak and helpless. She walked with great care, and required some support. During the last month she remained in a padded room, unable to walk, but occasionally she crawled to the door. She gradually became worse, and died January 17th, 1892, being then 49 years of age.

Although the patient had lived with a man prior to her admission into Colney Hatch, it is not clear that she was married, and two children whom she was accustomed to speak of as her own were apparently those of her sister. This sister was said to have very much the appearance of the patient, but had more colour; her voice, too, was said to be a little thick.

The patient slept well, but not heavily, and she never complained of headache. She was naturally good-tempered, and never complained; the latter doubtless with the hope that she would thereby be allowed to go home sooner; a wish that showed itself by her always writing to her sister, when she heard that she was coming to visit her, asking her to bring a bonnet and shawl in order that she might go back with her. She was irritable, however, if directly opposed at any time, and would then become restless and wander about. Her memory was by no means bad up to almost the last. She remembered very little things that had occurred years before. As an instance of this, it may be mentioned that about eighteen months ago her photograph was taken with much difficulty; when asked a few weeks before she died if she would like her photograph taken, she recalled every incident of the past occasion; the trouble she gave, and the names of those who held her and of those who were present. Hearing and eyesight were good; tactile sensation did not appear much impaired, and she never complained of numbness or tingling in the legs or hands. Her voice latterly was slow and thick, but she could be easily understood; during the last two weeks she seldom spoke. Her skin was very white, with entire absence of colour in her cheeks. There was no apparent scaliness of the skin, but there was a slight greasy appearance. There had never been an attack of erysipelas. At no time was there profuse perspiration, but occasionally beads of sweat were seen upon the head.

Her body temperature was never taken except when she had one of her bad attacks, when it was usually 100° F. Her bowels were generally somewhat confined; there was never diarrhœa. More recently micturition had been frequent, and she passed a considerable quantity of pale-coloured urine, which scalded. On several occasions it had been tested, although not during the last month or so, and no albumen was found. Catamenia were regular up to two years ago, since which nothing had been seen.

During the time she was in the asylum, she had several "seizures," and lost consciousness. The last occasion was three months before death, when she was unconscious about half an hour, and lost power on the left side of the body, from which, however, she quite recovered. Before this she had not had an attack for twelve months, and that time she had loss of power in the right arm following convulsions and foaming at the mouth. She was in bed then for six weeks.

For several years past there had been times when she was not so well; these were usually during the colder months of the year. Her face and limbs were then more swollen, blue and cold, and her breathing became more difficult, with some bronchitis. These attacks lasted only a week or two; improvement appeared to follow the use of jaborandi.

Her appetite was fairly good, but latterly she had some difficulty in swallowing food. She had gin to drink.

Post-mortem Examination (30 hours after death).—The general appearance of the body was that of well-marked myxœdema. Very obese. The weight was probably between 11 and 12 stone. All parts of the body swollen.

The skin was rough and coarse; the features blunted; lips, ears, nose, etc., thickened; eyelids (especially lower) swollen and œdematous. Hair on head dark and scanty, and was scanty on other parts of the body, but there was some hair on the upper lip. The abdomen was large and distended.

Fat.—There was a large amount of subcutaneous fat, which was of a pale colour and somewhat œdematous in appearance. This appeared to be uniformly the case over the whole body. There was much sub-peritoneal fat situated in the omentum; also much retro-peritoneal fat. This latter was also pale in colour, and was most markedly œdematous.

Muscle.—All the muscles of the body were of a very pale colour. This was seen to be the case with the pectorals and in the muscles of the anterior abdominal wall, psoas muscle, and some muscles of the legs and arms where incisions were made. The muscles in front of the larynx and trachea also pale.

Abdomen.—There was no fluid present in the peritoneal cavity.

State of Intestines.—The stomach and both large and small intestines were greatly and uniformly distended with gas.

Pelvic Organs.—The uterus and ovaries were of normal size, and apparently healthy. The bladder was contracted and empty.

Liver.—The liver was of about normal size and weight, and on section was dark and congested. The gall bladder contained bile.

Pancreas.—Nothing abnormal was noted about the pancreas.

Spleen.—Spleen was small, firm, and dark.

Suprarenals.—Both suprarenal bodies were apparently healthy. They seemed to be of normal size and consistency.

Kidneys.—The kidneys were of equal size, which was about normal; on section they were dark and congested, with slight thinning of the cortex; on removing the capsules the surfaces were found slightly granular. Each kidney contained one small infarct which was slightly raised above the level of the surrounding cortical surface, and measured $\frac{1}{4}$ inch across. Consistency of kidneys was firm.

Thorax: Serous Cavities.—The ribs were of normal hardness. On opening the pericardium it was found full of clear serous fluid. There were no pericardial adhesions, old or recent. No fluid was present in either pleural cavity. Firm old adhesions existed on the left side at the base and posteriorly.

Lungs.—Both lungs were rather larger than natural, especially the left. On section the lungs, which were of dark colour, had a firm appearance, as though due to solid œdema. The lower lobe of the left lung was the more solid, but did not sink in water. There was no pneumonic consolidation.

Heart.—The heart was considerably enlarged. This enlargement was dependent mostly on hypertrophy of the left ventricle. The dilatation, which was comparatively slight, was more of the right auricle than elsewhere. The myocardium was firm, of a healthy dark colour, very different from the pale colour of the skeletal muscles. The left ventricle was $4\frac{1}{4}$ inches in length, it contained no fat in its wall, which in its greatest thickness was $1\frac{1}{4}$ inch. The right ventricle had fat in its outer coat, replacing the muscular tissue, the latter being much thinned down, especially towards the apex; here the total thickness of cardiac wall was $\frac{1}{2}$ inch, of which half was represented by fat. There was a large accumulation of gelatinous-looking darkish yellow fat at the auriculo-ventricular furrows. This was most marked at the base of the right ventricle. The thickness of the right ventricular wall was here $1\frac{1}{4}$ inch, $\frac{3}{4}$ inch of which consisted of the fatty tissue. There was no clot or fluid blood present in the heart. All the valves appeared healthy, but the flaps of the bicuspid were fixed back: there was no atheroma. The foramen ovale was not completely closed.

Blood-Vessels.—The coronary arteries were atheromatous. The right, which passed through the mass of fat, was much calcified.

There was a calcareous plate in the aorta just above the valve, and the aorta was much calcified, especially at the lower part of the abdominal portion just above its division; here, too, the wall was almost destroyed through its entire thickness.

Tongue, etc.—The tongue was large and pale. Nothing abnormal was noticed about the pharynx, larynx, trachea, and œsophagus.

Thyroid.—The thyroid body could not be felt through the skin, nor could it be made out through the muscles covering it after the skin had been dissected off. On careful dissection, however, it was found to be present, though much diminished in size. It was uniform in shape, and there was absence of the isthmus, the lateral lobes uniting in the median line. It was very soft, with a few harder nodules felt in places, and was of a pale pink colour, making it somewhat difficult to distinguish from the pale muscles covering it. There had been a slight hæmorrhage at the upper border of the left lobe, $\frac{1}{2}$ inch from the middle line. The depth of the thyroid in the median line was exactly an inch, its lower edge being just above the fourth ring of the trachea. The lobes were of equal size, and measured $1\frac{1}{4}$ inches across at the upper part, the total breadth of the thyroid being therefore $2\frac{1}{2}$ inches. The breadth across the lower part was $1\frac{1}{2}$ inches. Both lobes measured the same in their longest diameter (obliquely, from above downwards). In its thickest part it was not more than $\frac{1}{4}$ inch. There were no outlying accessory parts of the thyroid seen.

Brain.—Calvaria thickened, membranes not thickened, but there was a considerable amount of fluid within the skull. There was slight atheroma of the vessels at the base of the brain.

The brain was of fair size and well developed. The ventricles were not dilated. The brain substance was firm, but did not appear abnormally hard. Situated in the left cerebral hemisphere, at the posterior part of the posterior limb of the internal capsule, was an old hæmorrhage, which had spread into the lenticular grey nucleus. The brain tissue was broken down, and of a brownish colour; it was $\frac{1}{3}$ inch in diameter, but softening extended beyond this. Also on the right side of the pons varolii a little anteriorly, and about half-way from above downwards, there was a small dark area $\frac{1}{8}$ inch in size, undoubtedly the result of an old hæmorrhage.

Pituitary.—On examining the base of the skull it was seen that the dorsum sellæ of the sphenoid bone, with the posterior clinoid processes, had a more backward direction than is usual, and this part of the sphenoid bone was found to be disarticulated. The pituitary body did not project above the level of the bone. After removal, which was effected with ease after removing the loosened bone posteriorly, the pituitary body was found markedly enlarged. It was oval in shape, measuring $\frac{3}{4}$ inch transversely, and $\frac{1}{2}$ inch antero-posteriorly, and was hollowed out above. The enlargement, which was uniform, was seen to be entirely dependent on an increase of the anterior lobe, and appeared to be due to hypertrophy of that portion.

The following are the weights of the various organs:—

Thyroid body, ...	188 grains.
Pituitary body, ...	19 „ (1·21 grammes).
Brain, ...	38 ounces.
Heart, ...	18 „
Left lung, ...	$20\frac{1}{4}$ „
Right lung, ...	13 „
Liver, ...	$47\frac{1}{2}$ „
Kidneys (each), . . .	$3\frac{3}{4}$ „
Spleen, ...	$3\frac{3}{4}$ „

(For the microscopic examination of these organs, see p. 235 *et seq.*)

Case 2.—*Myxœdema.*

We are indebted to Dr. C. W. Suckling for the brief notice of this case. Dr. Suckling has kindly informed us that since the Report of the Committee of the Clinical Society on Myxœdema was published, in which his cases appeared, he has had another fatal case of myxœdema. In this "the pituitary body was distinctly enlarged," and the thyroid atrophied. The notes of the case, however, he has unfortunately mislaid.

Case 3.—*Sporadic Cretinism.*

For the following notes of a case of sporadic cretinism that occurred in the Sussex County Hospital we are indebted to Dr. A. J. Richardson, of Brighton.

History.—H. V., a female child, aged 9 years, had its development arrested at 12 months. Cancer and consumption exist on the mother's side. There were three other children, all of whom were healthy. The patient has had hooping-cough, measles, and chicken-pox. During the last fourteen days there has been marked wasting and diarrhœa at times.

Condition.—December 3, 1891.—The child is 30½ inches in length, and does not look more than 3 years old. The bony skeleton throughout is very strong and stout. Head not particularly wide, but flattened to some extent, and the forehead low. The anterior fontanelle is ossified and depressed. The nose flattened, and the bridge much depressed, the shape suggesting congenital syphilis; lips protruding, teeth set far back and decayed, hair spare, dark, and wiry; pupils equal and normal, and brownish-green irides; tongue slightly protruding; neck very short, and thyroid body cannot be felt; ribs firm, and slightly nodulated; abdomen prominent, and a hernia protrudes from the umbilicus when the child cries; heart and lungs are apparently healthy; the limbs are short and strong, both arms and legs are bowed; the hands are large, flat, and podgy, but are not typically spade-shaped; the skin is dry, scaly, and of a brownish earthy hue—that over the lower extremities is shiny and wrinkled. The child has a vacant expression, and generally lies on its side. It is completely demented and cannot talk, but has a deep, rough, raucous cry. Co-ordination of movements are very slightly developed; patient can stand, but cannot walk without support; it crawls on the left knee and right foot, its progress being sideways. It is, however, able to get from the crawling position into the erect if it has something to climb up. The child's habits are dirty, and it passes everything under it.

December 22.—Up to yesterday there had been no change. Always taken food very badly. The temperature has varied from 96·2 to 96·8, and has never been above the latter. Yesterday there were several convulsions, each lasting a few seconds, during which the pupils were widely dilated, with no corneal reflex, and both arms and legs were in a state of tonic spasm. Unconsciousness remained for some hours. To-day several fits occurred, in which the limbs were at first jactated, and then seized by tonic spasm, pupils widely dilated, eyes at first converged to the right side, but afterwards to the left. The face is drawn to the right, and is blanched. Corneal reflex sluggish. Breathing is abnormal, inspiration being short, and expiration long and groaning. The abdomen is much distended, but moves with respiration. Respiration gradually became more shallow, pulse ceased, and the patient died.

Post-mortem.—The body presented general malformation, and was badly

nourished. Cranial bones hard; no diploë present. The dura mater was adherent to the bones throughout, and the subdural space was small.

The brain was uniformly developed, the convolutions well defined, the grey matter softish and œdematous-looking. Three months after being kept in preserving fluid the brain weighed $28\frac{3}{4}$ oz., and no naked-eye lesion was found internally. Nothing abnormal was noted about the pons, medulla, or cerebellum.

The pituitary body was found to be abnormally large, of which the accompanying outline is an exact tracing.

The thyroid gland was carefully looked for, but no trace of it could be found, and it was therefore considered to be entirely absent.

The thymus was absent; the pleuræ were healthy, but there was œdema at the base of both lungs; heart healthy; small intestines distended with air, and pale; liver normal; spleen very small, being only two inches in longest diameter; kidneys lobulated, but otherwise normal.

The brain and photographs of this case were shown at the Brighton and Sussex Medico-Chirurgical Society, on February 4th, 1892.

The Hypophysis Cerebri.

In the recent state the weight of the hypophysis obtained from the myxœdematous patient (Case 1) was 1·21 grammes. In Quain's "Anatomy" the weight of this body is given as from ·3 grammes to ·6 grammes. Professor Thane has kindly informed us that the weight given by Vierordt in his "Anatomische Tabellen" of 1888 is ·5 grammes, whilst that of Testut ("Névrologie," 1891) is from ·35 to ·45 grammes. In an analysis of fifty cases from women we obtained the slightly higher average of ·6 grammes. We may yet find, however, that this slight increase was abnormal, owing to the fact that the glands were obtained from the insane. The ages of our subjects varied from 31 to 84, and the highest and lowest weights were respectively ·896 and ·384 grammes. From these figures it will be seen that the enlarged pituitary from the above case was fully double the average weight. In this connection it may be observed that the actual weight increase of the hypophysis after thyroidectomy in rabbits is, according to the figures of Hofmeister[1] and Stieda,[2] slightly under the double. Thus, according to Hofmeister, the weights of the pituitary body, from two to five months after the operation, were ·032, ·025, ·039, ·040; whilst in the control animals the weights were, in the same order, ·019, ·015, ·022, ·018. Similarly the figures given by Stieda are, after the lapse of one to twelve weeks, ·014, ·027, ·012, ·02, ·028, ·025, and in the control animals, ·012, ·021, ·012, ·018, ·013; difference, ·002 to ·012 grammes.

[1] Hofmeister, *Fortschritte der Medicin*, No. 4, 1892.

[2] Stieda, "Ueber das Verhalten der Hypophysis des Kaninchens nach Entfernung der Schildrüse," Ziegler's *Beiträge*, Band x.

The photographs (Figs. 1 and 2 in the text) show a uniform but slight enlargement in all directions. In a median, vertical, antero-

FIG. 1.—Hypophysis, natural size. Seen from above, showing attachment of infundibulum.

posterior section, it is seen (Plate XVIII., Fig. 1) that only a small part of the section, *a*, represents the posterior lobe, the rest consisting of the

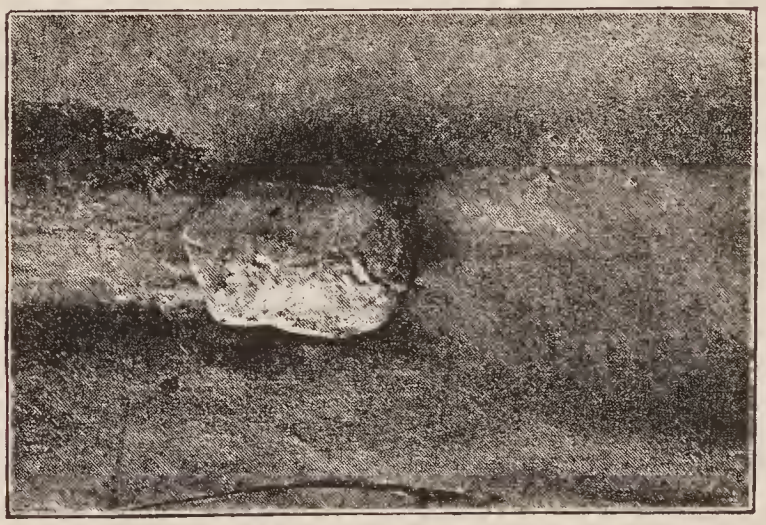


FIG. 2.—Hypophysis, natural size. Seen from below. *N.B.*—The antero-posterior diam. is much shorter than the transverse.

hypertrophied anterior lobe. The anterior lobe has every appearance of activity; many of the lumina of the acini are filled with colloid material (stained blue by Gerrard's logwood and red by eosin, after hardening in Müller's fluid), whilst posteriorly, in immediate contact with the posterior lobe, there is very considerable cystic dilatation. A small portion of this area is seen in Plate XVIII., Fig. 2. Still more noteworthy, perhaps, is the increase of extra-acinar colloid-like material, the latter being found with considerable frequency in the neighbourhood of the root of the infundibulum, in what appear to be either thin-walled venules or lymphatic spaces. Many of the spaces are, for the most part, occupied by the colloid-like material, a few red corpuscles being scattered or grouped in it (Plate XIX., Fig. 3).

There is a very noteworthy increase in the size of the cells composing

the acini, and their contours are often very irregular; the acini, as a whole, appearing in consequence more irregular and less defined than normal. In one narrow marginal region, on the upper surface of the gland, the nuclei failed to stain with the logwood, and they moreover showed the peculiar pathological alteration of a thickened refractive margin. In some of the cells vacuolation was present, but it was very limited. We could not observe any fatty degeneration.

The stroma is not increased in amount, but presents a clear and loose appearance in common with the connective tissue elsewhere. As is well known, the vessels of the pituitary body are numerous and thin-walled; we observed no increase or diminution in their number; in the anterior portion of the gland several of the capillaries are distended with red corpuscles, whilst at the root of the infundibulum, as previously mentioned, what appear to be capillaries or vēnules contain a colloid-like substance. The larger vessels are the seat of an endarteritis, a part of the general arterio-capillary fibrosis; the endarteritis is, however, not so marked as in many other organs—as in the brain itself, for instance.

In contrast to the anterior, the posterior lobe is atrophied and pressed upon by the cystic spaces previously mentioned; the upper portion of the lobe is occupied by colloid-like (? plasmatic) material, which is not bounded by a cell membrane. The rest of the lobe appears less cellular, and the interstitial substance more granular, than is the case in the normal hypophysis.

We may now conveniently compare the above appearances with those observed by various authors in the diseased and healthy gland and in glands in the lower animals in which the thyroid has been extirpated.

Rogowitsch[1] was the first to observe an increase in size of the pituitary gland after thyroidectomy in rabbits; he, however, refrained from stating the actual increase in weight or size. He describes three principal types of cell—(1) the chromato-phile cells of Flesch, which colour yellow with picro-carmine and resemble pancreas cells; (2) the "chief cells," which stain red with picro-carmine, are clear, and form the majority of the gland; (3) nuclear foci. He further describes vacuolation, but apparently not in the cell substance, and colloid-like material in the vessels; he also lays stress upon the "medullary layer" and upon the gross anatomy of the gland. After thyroidectomy he describes increased vacuolation, enlargement of the chief cells, and increase of the extra-acinous colloid-like substance and the presence of large granule cells.

Stieda,[2] on the other hand, describes the hypophysis of thyroidectomised rabbits as "merklich vergrossert," and gives the previously

[1] Ziegler's *Beiträge*, Band iv.; and *Centrlb. f. d. med. Wissensch.*, 1886; and *Archives de Physiologie*, 1888.

[2] *Loc. cit.*

mentioned weights. He describes hypertrophy of the "chief cells" and vacuolation of the chrome cells.

In Hofmeister's[1] rabbits the hypertrophy, as seen above, is even greater than in Stieda's cases. He agrees with the former observers in recording increase of the "chief cells" and of the vacuolation.

Pisenti and Viola[2] give a short description of the normal and pathological pituitary body in the human subject. They lay considerable stress upon the presence of extra-follicular colloid-like material, both in spaces forming a locular system in the interstitial tissue and in the blood-vessels. In a case of a woman who died of cancer, and in whom the thyroid was the seat of a *struma fibrosum*, there was a very considerable increase in the amount of colloid-like substance in the gland acini, in the inter-follicular spaces (many of which were cystic), and in the vessels.

In the hypophyses which we have examined so far,[3] we have been unable to observe any definite divisions of the gland substance. Cystic dilatation, though very marked in the myxœdema case, can usually be seen to a slight extent in the most posterior part of the anterior lobe. Perhaps this region of cystic dilatation may correspond to the "medullary" layer. Pisenti and Viola believe that the colloid cystic dilatation is interstitial. We will not deny that this may be the case with some of the dilated cystic cavities in our case of myxœdema, but, as the majority are lined with a cubical epithelium, it is more probable that they are dilated gland acini. We would again emphasise the fact that, in the case of the myxœdema patient, the increase of colloid-like material was strikingly great in comparison with other normal control cases which we examined. We found it impossible to distinguish, with any degree of certainty, more than one type of gland cell; we only observed the great increase in size and the increase of irregularity.

The actual number of cases in which increase in size or alteration in structure of the pituitary body has been noted in cases of disease or atrophy of the thyroid is not great. As just mentioned, Pisenti and Viola described increased colloid formation in a case of struma fibrosum. Bourneville and Bricon[4] observed hypertrophy in a case of sporadic cretinism with loss of the thyroid, the hypophysis measuring 15 to 16 mm. in width and 1 cm. in height; to this case we may add our own (Case 3). Dolega,[5] in describing a cretinoid skull, points out that the pituitary fossa was larger in proportion to the rest of the skull; in this case there was marked atrophy of the thyroid gland.

A search through a large number of cases of myxœdema reported at

[1] Hofmeister, *loc. cit.*

[2] *Centrlb. f. d. med. Wissensch*, 1890.

[3] We are at the present time continuing our examination of the hypophysis in various conditions.

[4] *Archives de Névrologie*, 1886.

[5] "Ein Fall von Cretinismus beruhend auf einer primären Hemmung des Knochenwachsthums," *Ziegler's Beiträge*, Band x.

home and abroad, and of the Clinical Society's Report of 1888,[1] and of Mosler's,[2] Bircher's,[3] and Hunn and Prudden's[4] more detailed descriptions, failed to yield other than negative results. In a large number of post-mortems but scant attention has evidently been paid to the state of the hypophysis. On p. 39 of the Clinical Society's Report it is stated that "other parts of the intracranial contents, including the pituitary body, were also examined in solitary instances, but the sub-committee failed to discover any pathological change." In this connection Dr. Hadden, who then acted as honorary secretary, has kindly informed us that at the time the committee met they had notes of more than thirty fatal cases, and that since then he had himself made occasional post-mortems, but in no case was the pituitary enlarged. In Prudden's very careful report of the anatomical changes in two autopsies no mention is made of the hypophysis. Dr. Barling published a necropsy in the *Lancet* of 1886, and investigated the pituitary microscopically; in reference to this case he has kindly informed us that the pituitary was not larger than it generally is, and that he regarded it as quite normal. Drs. Duckworth, Ord, Shelswell, Whipham, and Whitwell, who likewise had had opportunities of making post-mortems, kindly informed us that in those cases in which they had examined the pituitary they did not observe any abnormality. We venture to think, however, that an increase in size, like that in our case, might easily be overlooked unless special attention were directed to it; moreover, a careful microscopic examination has rarely been made.

As is well known, enlargement of the hypophysis is one of the most striking features in acromegaly; the thyroid also may be hypertrophied, atrophied, or the seat of a goitre. It occurred to us therefore to try and find out whether the enlargement of the hypophysis was compensatory to an atrophied or otherwise diseased thyroid, or whether it was merely part of a general hypertrophy of the thyroid-like tissues. In the first place it may be pointed out that the hypertrophy of the hypophysis is probably limited to the anterior lobe, for here again, although several autopsies have been made, a minute examination of this structure appears not often to have been carried out. Recently, however, Marie and Marinesco[5] have described a case of acromegaly in which there was simple hypertrophy of the thyroid and thyroid-like tissue of the hypophysis. Their figures of the latter structure show that the cells were hypertrophied and more irregular, and that in some the nuclei had disappeared. They stated that they

[1] "Pathological Report of the Committee of Clinical Society of London, to investigate the subject of Myxœdema," 1888.

[2] Mosler, "Ueber Myxœdema," *Hahn's und Fürbinger's Sammlung*, Heft 14.

[3] Bircher, *Volkmann's klin. Vort.*, No. 357, 1890.

[4] Hunn and Prudden, "Four Cases of Myxœdema with two Autopsies," *Int. Journ. Med. Sciences*, July 1888.

[5] Marie and Marinesco, "Anatomie pathologique de l'Acromegalie," *Archiv. de méd. exp.*, 1891.

could not differentiate between the chromophilous and maternal cells. On the other hand, Bury[1] describes a case in which he states the thyroid was enlarged and contained a cyst in each lobe, and the pituitary was the seat of a large *gliomatous* tumour. We may point out, however, that a gliomatous tumour, unless defined, may mean anything.

To return to the apparently associated changes in the thyroid and pituitary in acromegaly. Souza-Leite,[2] in his well-known collection of cases, states that atrophy of the thyroid is more frequent than hypertrophy; from this one might perhaps be justified in saying that in the cases collected by him a hypertrophied hypophysis was more frequently associated with an atrophied thyroid. Atrophy of the thyroid also appears to have been present in cases recently described by Redmond, Kanthack, Phillips, Hadden, Ballance, and Virchow[3] (only one autopsy). On the other hand, there have been several cases of hypertrophy of the thyroid, with associated enlargement of the hypophysis; amongst these may be mentioned Henrot's[4] and Godlee's[5] well-known cases, and those of Bury[6] and Holsti.[7]

In order, if possible, to come across further cases of compensatory hypertrophy of the hypophysis, search was made through the more noted records of cases of *cachexia strumipipriva operativa*, and of tumours of the pituitary and thyroid bodies. Search through the reports of autopsies of cases of *cachexia strumipipriva operativa*, made by Grundler,[8] Reverdin,[9] Bode,[10] and others resulted negatively. Professor Horsley, however, kindly wrote to Professor Kocher, who replied that he had found changes in the pituitary gland to such an extent, that one of his students was working upon the subject. We may also mention that nothing bearing on this point can be found in Kocher's very detailed paper in *Thiersch's Festschrift* (1892): "Zur Verhütung des Cretinismus u. Cretinoider Zustände nach neuen Forschungen."

Observations upon tumours of the hypophysis date far back; thus Wenzel[11] tried to connect epilepsy with diseases of the hypophysis, and Friedreich[12] to formulate the symptoms of growths of the pituitary region. Virchow[13] described glandular overgrowth well under the term, *struma pituitaria*. Numerous other cases have been described and collected

[1] Bury, *Lancet*, 1891, vol. i., p. 1383.
[2] Souza-Leite, "L'Acromegalie," Paris, 1890.
[3] Virchow, *Berl. klin. Wochensch.*, No. 5, 1889.
[4] Henrot, "Notes de Clinique médicale," Reims, 1877.
[5] Godlee, *Clin. Soc. Trans.*, 1888.
[6] *Loc. cit.*
[7] Holsti, ref. in *Archives de. méd. exp.*, 1891.
[8] Grundler, *Beiträge zur Brune*, Tübingen, 1884.
[9] Reverdin, *Rev. méd. de la Suisse Romande*, 1887.
[10] Bode, *Berliner Klinik*, 1892.
[11] Wenzel, "Ueber den Hirnanhang fallsüchtiger personen," Mainz, 1810.
[12] Friedreich, "Beiträge zur Lehre von den Geschwülsten innerhalb der Schädelhöhle," Würzburg, 1853.
[13] Virchow, "Die krankhaften Geschwülste."

by Müller,[1] Eisenlohr,[2] Arnold,[3] Weichselbaum,[4] Ribbert,[5] Breitner,[6] Heusser,[7] Sibley,[8] and other cases are to be found in the leading text-books, and in the various medical transactions. Wassiljew[9] describes the changes in the pituitary body in disease of the brain and membranes. An analysis of these cases shows that adenomatous hypertrophy (from the size of a pigeon's egg to that of a green walnut) is by far the most frequent neoplastic change in the hypophysis. Increase of the colloid material and the formation of colloid cysts is very common; in many cases the cells are larger and more irregular. Many of the tumours were found in aged subjects, and in some cases there was epilepsy, insanity, or marked evidence of mental decay. In none of the cases, however, which we examined, was the condition of the thyroid noted. We ourselves had an opportunity of examining an enlarged hypophysis. The tumour was taken from a female, æt. forty-three, who died of extensive recurrent cancer of the breast. Some of the organs contained secondary deposits, all the other organs are described as healthy, but as their names are not given it would be impossible to say whether the thyroid was examined. The pituitary body is about the size of a pigeon's egg, and in the recent state presented a pinkish yellow appearance on section; the enlargement is wholly in the anterior lobe; the posterior is atrophied and projects into a cystic cavity. The acini are closely set, and the cells are about the normal size; there are no colloid nodules or collections, either extra- or intra-acinar, and the cystic cavity is not filled with colloid. This form of enlargement, it will be observed, therefore, contrasts with that which we described in the case of myxœdema.

It lastly remained for us to examine whether an enlarged hypophysis had been encountered in the numerous cases of thyroid tumours collected by different observers.[10] This search, however, failed to yield any positive result.

Examination of other Tissues from a Case of Myxœdema. (*Case* 1.)

We may now, in conclusion, give a short description of the microscopical changes which we found in the *thyroid*, *kidney*, *lung*, *liver*, *brain*, *skin*, *muscle*, and *heart*. Portions of the organs were hardened in Müller's fluid, and stained with logwood.

Thyroid.—The changes present in the thyroid are those that are held

[1] Müller, "Ueber Entwick. u. Bau der Hypophysis," etc., *Jenaische Zeitschrift*, 1871.

[2] Eisenlohr, "Zur Casuistik der Tumoren der Hypophysis," *Virchow's Archiv*, Band lxviii.

[3] Arnold, "Adenoma der Glandula pituitaria," *Virchow's Archiv*, Band lvii.

[4] Weichselbaum, "Zu der Neubildungen der Hypophysis," *Virchow's Archiv*, Band lxxv.

[5] Ribbert, "Ein Tumor der Hypophysis," *Virchow's Archiv*, Band xc.

[6] Breitner, "Zur Casuistik der Hypophysistumoren," *Virchow's Archiv*, Band xciii.

[7] Heusser, *Virchow's Archiv*, Band cx.

[8] Sibley, "Adenoma of the Pituitary Body," *Path. Soc. Trans.*, 1888, with references.

[9] Wassiljew, ref. in *Neurolog. Centralb.*, 1888.

[10] Braun, "Struma maligna," *Langenbeck's Archiv*, 1883, and Cramer, "Struma maligna," *Langenbeck's Archiv*, 1887.

to be typical of the atrophied gland in myxœdema, and which have been described both in the Clinical Society's Report and by Prudden (*loc. cit.*). The gland tissue was represented by a few scattered nodules, from a pin's head to a millet seed in size. On microscopical examination these proved to be (Plate XIX., Fig. 4) groups of lymphoid corpuscles, infiltrating the necrosing gland elements. In eosin-logwood preparations the former corpuscles stained deep blue, whilst the necrotic epithelium assumed a beautiful rose tint. In still more advanced parts there were no corpuscles, and the gland nodules were represented by hyaline masses. Throughout the gland there was the most pronounced endarteritis and hyaline periarteritis, the smaller vessels were completely occluded, whilst the walls of the larger were enormously thickened (Plate XIX., Fig. 5). The interstitial connective tissue had the typical loose appearance seen in cases of myxœdema. In one or two places at the periphery there were a few groups of gland acini quite unlike adult thyroid acini. They were solid, and composed of numerous small gland cells, staining deeply with logwood; they had the appearance of proliferating acini. In another place, also at the periphery, there was a group of small cystic spaces lined by deeply staining small gland cells, and containing globules of colloid-like substance; these cystic acini were also unlike the normal colloid gland acini. The solid gland acini most probably correspond to the embyronic thyroid tissue, which, according to Wölfler's beautiful monograph,[1] is normally present at the periphery, both at the end of fœtal life, and even in the adult. According to this observer these acini serve as reserves of formative material; and it is not improbable that the cystic change above alluded to is a compensatory action on the part of this reserve material. An abnormal persistence and overgrowth of this fœtal tissue may perhaps also account for the appearance described by Hale White[2] in a case of myxœdema, where the acini were filled with large cells, and that described by Gulliver,[3] in which the thyroid was enlarged and the seat of a "carcinomatous infiltration"; also for that in one of Fagge's cases of sporadic cretinism in which the thyroid was "carcinomatous."[4]

There is a further explanation of these glandular cystic spaces. They may possibly represent duct structures. In connection with this point it must be remembered that in acute atrophy of the liver (red) and in the kidney, as one of us has had occasion to observe, whilst the glandular tubes undergo extensive necrosis the duct tubes proliferate.

Kidney.—Considerable endarteritis and periarteritis, with general fibrous tissue overgrowth. Foci of lymphoid infiltration in the vascular medullary rays close to the cortex. Renal tubules slightly dilated, epithelium in many cases flattened. A large proportion of the tubes

[1] Wölfler, "Ueber die Entst. u. den Bau der Schilddrüse," Berlin, 1880.
[2] "Clin. Soc. Report on Myxœdema."
[3] *Path. Soc. Trans.*, 1886.
[4] Shattock, *Lancet*, ii., 1885, p. 1044.

are filled with "colloid"-like globules, others with hyaline casts. Slight fibrosis of the glomeruli and their capsules.

Lung.—The lung had, in the recent state, a notable gelatinous feel, and on section this observation was confirmed by the thickened, loose appearance of the alveolar walls, septa, and pleura. There are some scattered foci of small round-celled infiltration in the alveoli, appearing for the most part to be peri-bronchial; many of the alveoli are filled with mucoid substance. The capillaries, whether from the looseness of the structure or from other cause, appear to be much dilated. The smaller and larger vessels exhibit a most marked endarteritis, some of the vessels are converted into apparently soft hyaline cylinders, others are represented by hypertrophied muscular and fibrous bands. Many of these endarteritic vessels give rise to psammoma-like projections into the alveoli, whilst closely connected with them lay, scattered here and there in the lung, *cartilage-like tumours*, concerning the origin of which we shall have something further to say in a subsequent paper.

Liver.—Considerable thickening of the portal canals. The connective tissue has, however, the loose characteristic form; in these canals the walls of the bile ducts, portal veins, and hepatic arteries are very considerably thickened. All the liver cells are slightly smaller than normal, and there are scattered patches of œdema and necrosis. Scattered throughout the liver are numerous dilated channels filled with a mucoid substance; whether these are dilated lymphatics, venules, or bile ducts it is very difficult to say. They are not lined by a definite epithelium.

Brain.—The most striking change in the sections of the white matter is the very pronounced endarteritis. The smaller and larger vessels are partly or completely occluded; there is also considerable periarteritis, and the surrounding brain tissue is pressed upon. This condition of the vessels is also found in parts of the cortex that were examined. The large pyramidal cells of the motor cortex were not examined, but from the condition of the blood-vessels, the vacuolation, etc., described by Whitwell,[1] are such as we should have expected to find. At the seat of the hæmorrhage into the internal capsule was a mass of hæmatoidin, and in the neighbourhood the perivascular lymphatics were filled with pigment. There was a very considerable amount of colloid material in many of the vessels and perivascular spaces.

Skin.—In a portion of the skin removed from the side of the neck, the epithelium is slightly atrophied; the sebaceous glands are numerous and conspicuous, many being widely dilated and filled with débris. The majority of the hair follicles appear atrophied, but at the mouths of some a broken swollen hair may be found; we came across one hair pearl deep in the corium. The errectores pili stand out prominently. The sweat glands are conspicuous, a circumstance partly due to the

[1] Whitwell, *British Med. Journ.*, 1892.

general looseness and clearness of the connective tissue. The connective tissue sheaths of most of the preceding epithelial appendages are thicker and more cellular than normal. Many of the vessels are endarteritic, and in some of the larger ones there is considerable hyperplasia of the various cell elements composing the wall. The condition of the connective tissue is that which has often been described; there are no dense trabeculæ, for these are replaced by exceedingly delicate bundles of fibrillæ with their nuclei, so that there is a distinct increase in the number of the connective tissue corpuscles. There is a notable increase in the ground substance. The fat cells are distinctly smaller than normal, a fact which has also been previously observed; but their nuclei almost invariably presented a very curious appearance owing to the presence of a larger or smaller *vacuole*. Many of the fibres of the platysma muscle are degenerated.

Muscle.—Sections from the pectoralis major showed slight swelling of the intermuscular connective tissue. The muscle fibres themselves appeared normal, except in a few cases. There was slight increase in the number of the muscle nuclei. The muscle *nerves* were distinctly swollen, and the nerve fibres themselves appeared much more loosely arranged than normal.

There was, in fact, considerable peri- and endo- neuritis; but we are, as yet, unable to say whether the "Blasenzellen," described first by Langhans,[1] and then by Kopp,[2] in *Cachexia thyreopriva* were present. According to these observers, there is, both in *Cachexia thyreopriva* in man, and in animals in whom the thyroid has been extirpated, a very marked gelatinous perineuritis, the chief characteristic of which is the presence of swollen uni- and multi- locular cells.

Heart.—Sections made through the wall of the right ventricle, at its base, show the following conditions:—A wide band of adipose tissue separates the muscle from the pericardial covering, the fat cells are somewhat small, and their nuclei almost invariably present the peculiar vacuolated appearance which has already been described. The pericardium is formed of a thick band of fibrous tissue, beneath which are masses of small round cells, forming a more or less continuous layer. The myocardium is replaced to a considerable extent by fat, the cells of which separate the small muscular bands from one another. The muscle fibre cells appear fairly healthy, their striation being about normal, but they are somewhat loosely arranged. There is nothing noteworthy concerning the endocardium, and this presents no collections of small cells. All the small vessels are endarteritic, and the transverse section of the coronary artery shows a marked atheromatous condition.

ADDENDUM.—Since completing the above paper we have heard from

[1] Langhans, "Uber Veränderungen in den peripherischen nerven bei Kachexia thyreopriva ü. Affen, sowie bei Kretinismus," *Virchow's Archiv*, Band cxxviii., May and June 1892.

[2] Kopp, "Veränderungen in Nervensystem besonders in den peripherischen nerven des Hundes, nach extirpation der Schilddrüse," *Virchow's Archiv*, Band cxxviii., May 1892.

Professor Horsley that he has been informed by Professor Kocher that Dr. Schönemann, under Professor Langhans, has completed a paper upon the changes in the hypophysis following extirpation of the thyroid. He has failed to find any compensatory increase of the hypophysis in goitre—that is, in cases of degeneration of the thyroid, or in cachexia strumpipriva; but he believes that an increase may take place in cases of hypertrophy of the thyroid gland.

DESCRIPTION OF PLATES.

Plate XVIII.

Fig. 1.—Antero-posterior section of the pituitary body. Natural size, and magnified about 10 diameters. The division between the anterior and posterior lobes is seen.

a. Colloid material in posterior lobe.
b. Colloid material in anterior lobe.

Fig. 2.—Section of the posterior part of the anterior lobe of the pituitary body stained with logwood. Obj. $\frac{1}{4}$ in. Pillischer. Well-marked dilatation of the follicles.

Plate XIX.

Fig. 3.—Posterior portion of the anterior lobe of the pituitary body. Stained with logwood. Obj. D. Zeiss.

a. Red blood-corpuscles.
b. Colloid material in the blood-vessel.
c. Colloid material in a gland acinus.

Fig. 4.—Section through part of the thyroid body, showing the edge of one of the nodules of lymphoid tissue, with the degenerated remains of the epithelium. Stained with logwood. Obj. $\frac{1}{4}$ in. Pillischer.

Fig. 5.—Blood-vessels and connective tissue of the thyroid body. Stained with logwood. Obj. $\frac{1}{4}$ in. Pillischer.

Fig 1

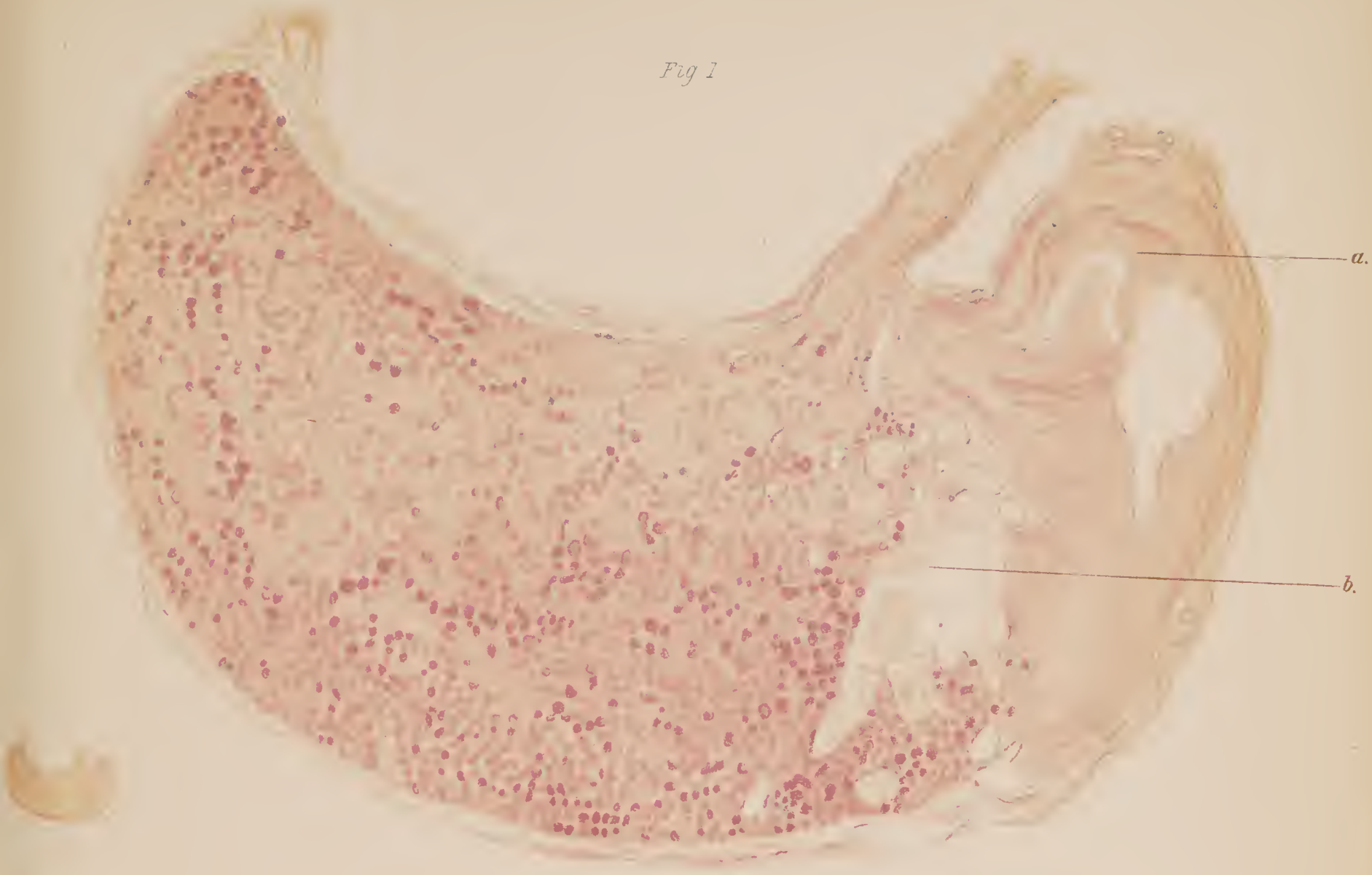


Fig 2

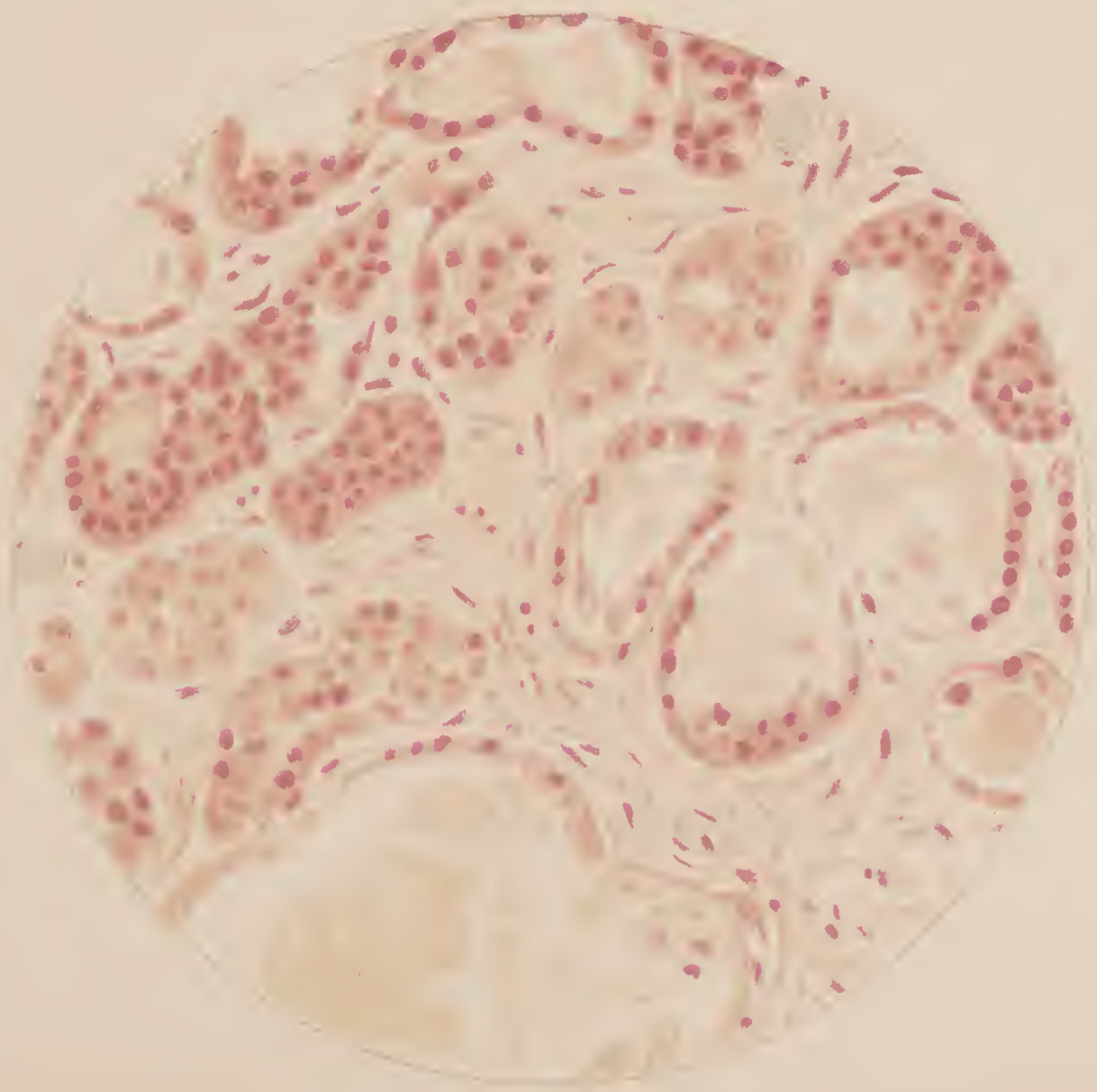


Fig 3

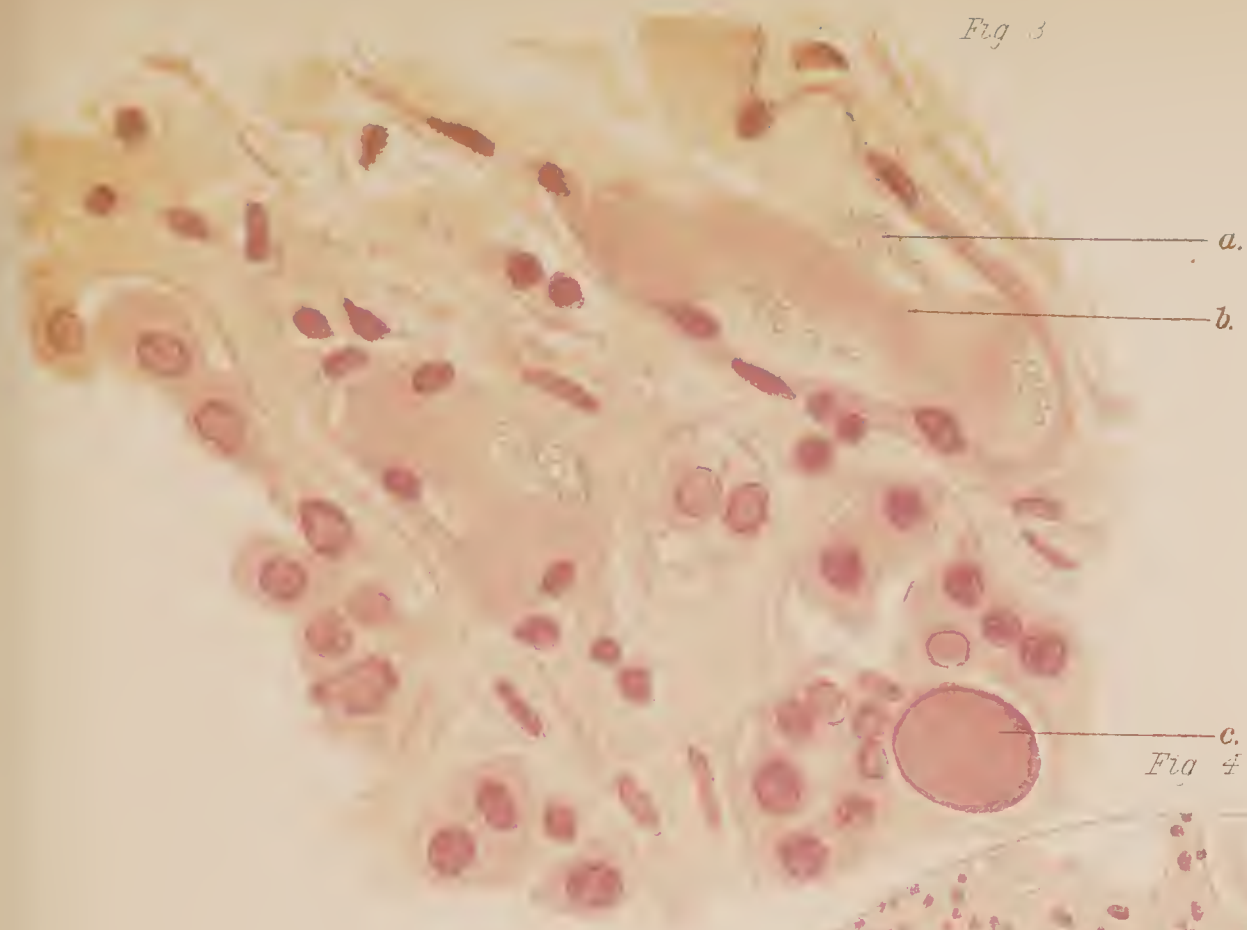


Fig 4

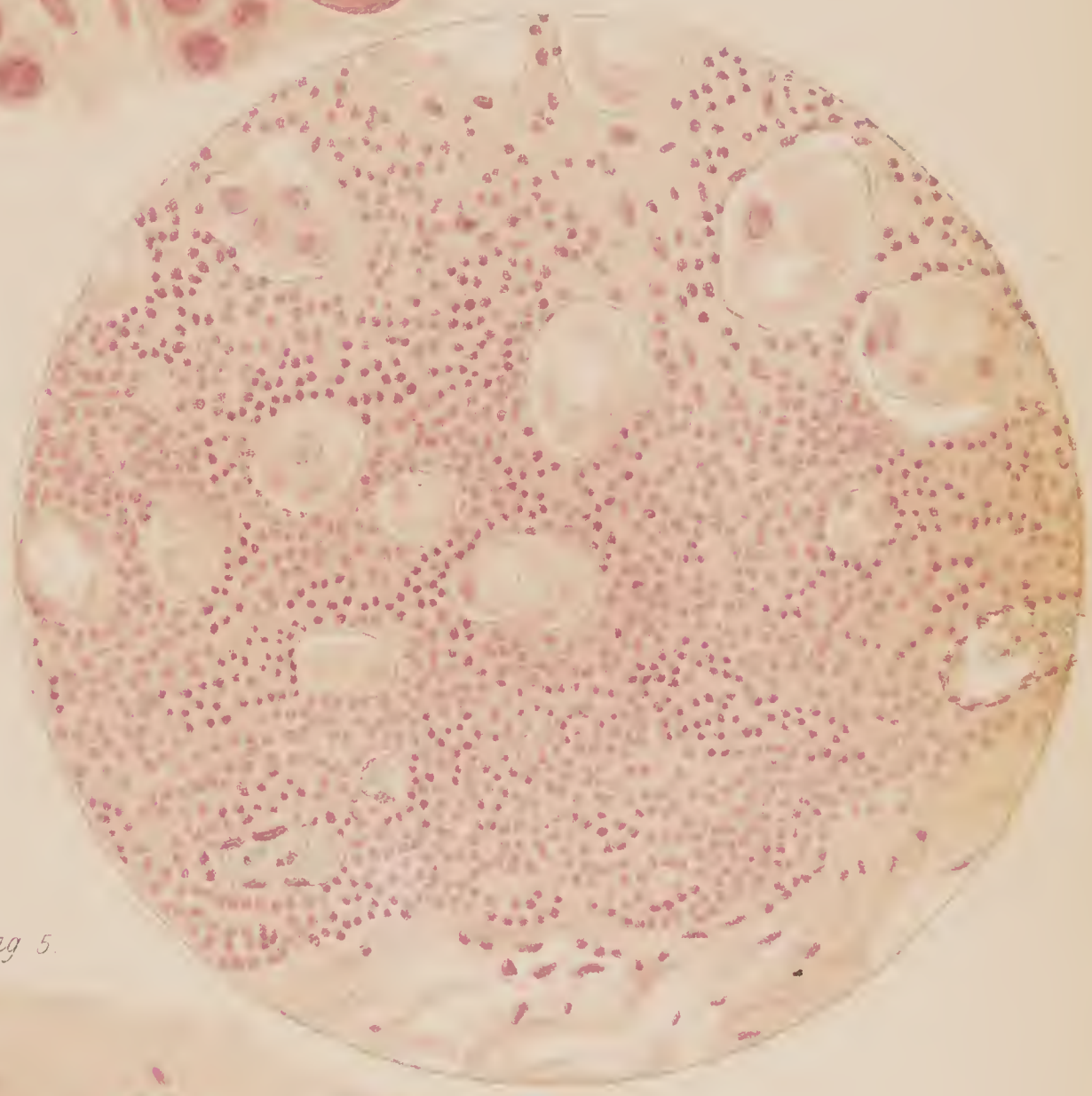
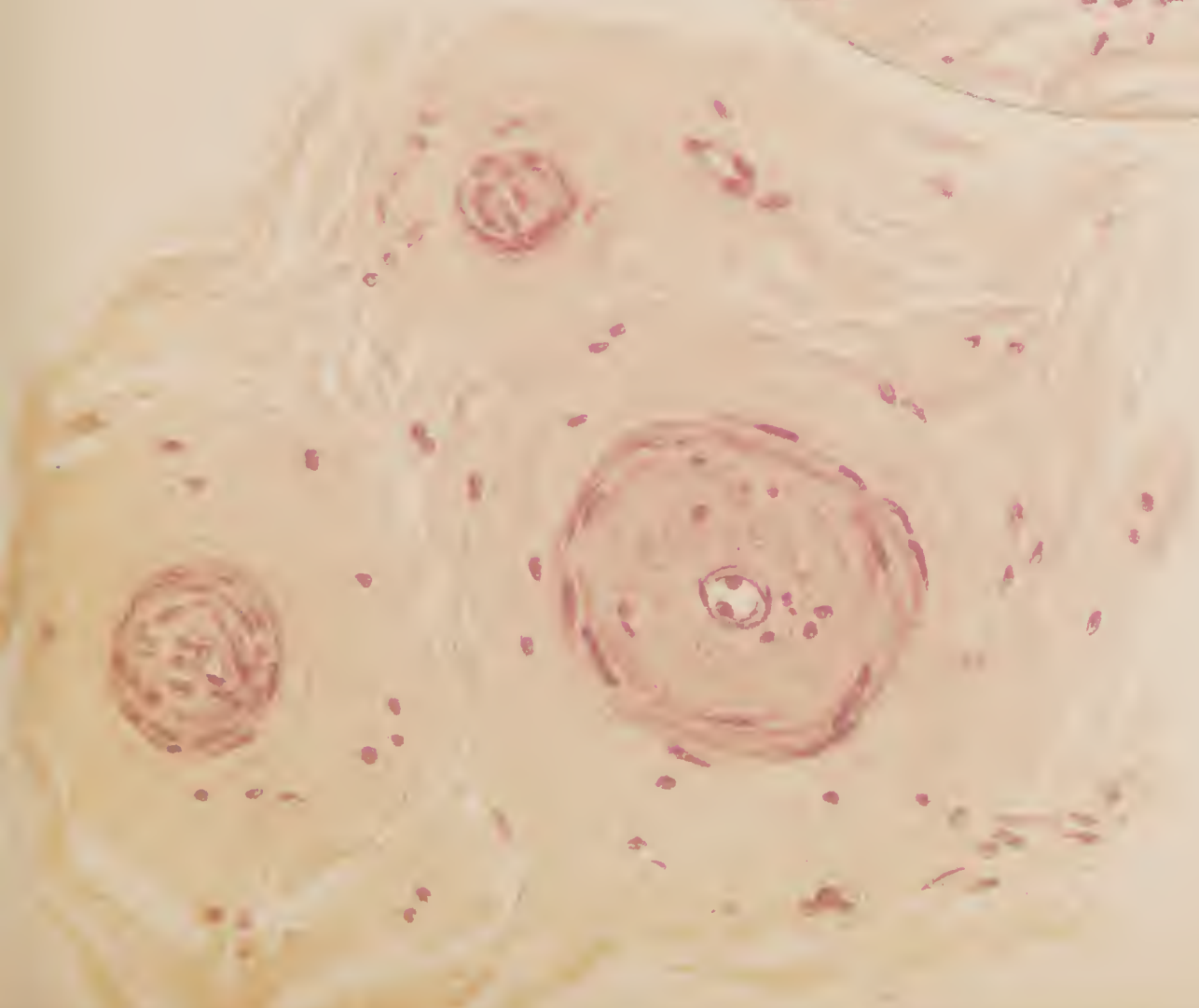


Fig 5



A FURTHER CONTRIBUTION TO THE STUDY OF THE PATHOLOGY OF THE HYPOPHYSIS CEREBRI.

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(Plate XXI.)

From the Pathological Laboratory of University College, London.

We have divided this second paper into 4 parts. Part I. An historical survey of the pituitary body, including (1) embryology, (2) anatomy and morphology, (3) function, and (4) pathology. Part II. The normal and pathological anatomy of the hypophysis cerebri, and the result of an examination of 100 pituitary bodies. Part III. The tumours of the hypophysis cerebri, of which we give 8 cases of our own. Of these, 6 are taken from an analysis of 3000 autopsies upon the insane, 1 a case of acromegaly. Appended are the references to some 90 additional cases. Part IV. Symptomatology.

In our first paper we recorded the experimental evidence in favour of the relationship of the gland tissue of the hypophysis cerebri and the thyroid, and we are now enabled to further add to it. We also recorded the enlargement of the hypophysis in 2 cases of myxœdema and in 3 cases of cretinism (our own and other cases); we further dwelt upon its conspicuous enlargement in acromegaly. We now record its enlargement in 1 case of cachexia thyreopriva and in 5 cases of cretinism. Lastly, we have brought together the neoplasmata of the hypophysis, which, in the vast majority of cases, are glandular or colloid cystic glandular tumours. With this evidence before us we hope to strengthen the evidence of a relationship which, we think, exists between the glandular tissue of hypophysis and thyroid, and the view of the participation which the hypophysis appears to share, to a certain extent in common with the thyroid, in the pathology of the group of diseases known as myxœdema, cretinism, and acromegaly.

I. Historical Survey.

Embryology.—In a short paper in *Müller's Archiv* for 1838, Rathke made known his views relative to the formation of the pituitary gland. In 1871 Wilhelm Müller[1] communicated his classic paper upon the comparative embryology of the hypophysis cerebri. He showed how the posterior lobe lost its nerve substance and became smaller as the scale of organisation was ascended; he pointed out the constant relationship of the anterior lobe to the carotid system and subclavian arteries; and, further, how the invasion of the rudimentary gland by vessels and connective tissue changed its configuration, and brought about the formation of solid branching epithelial tubes, which became cut off from the common duct. He concluded from his researches that the pituitary gland performed a special physiological function, for, unless this were so, how could it have maintained its definite characters in the animal kingdom from myxine upwards.[2] Further observations upon the embryology of the gland have been made by, amongst several others, Michalkowics[3] and Kraushaar.[4]

In 1882 Dohrn[5] put forward his very interesting theory, viz. that the gland was originally a paired organ formed in connection with pre-oral branchial fissures. As Lothringer[6] points out, this view is favoured by the fact that in the dog there is a more or less symmetrical lateral arrangement of the hypophyseal fissures (see later). The view is, moreover, interesting, because it tends to show a resemblance between the developmental history of the hypophysis and the thyroid.

Anatomy and Morphology.—We need only allude to some ancient and modern views as to the nature of the hypophysis cerebri, namely, as to whether it represented a vascular gland or a nerve gland; whether the notochord or pia mater formed it; whether it was the vestigial anterior terminal end of the spinal cord, or represented the œsophageal ring of a primitive alimentary tract. In 1860 Luschka[7] published a monograph upon the anatomy of the pituitary body, and strongly insisted upon the pia matral division between the glandular and nervous portions of the pituitary body. From this time the similarity of the structure of the hypophyseal gland and thyroid appears to have

[1] Müller, "Ueber Entwick. und Bau der Hypophysis u. d. Processus infund. cereb.," *Jenaische Zeitsch. f. Naturwiss.*, Bd. vi.

[2] As far as we can judge, this view does not seem to have been largely adopted by succeeding embryologists; the gland seems rather to have been regarded as a vestigial structure.

[3] Michalkowics, "Wirbelsäute u. Hirnanhang.," *Schultze's Archiv f. mik. Anat.*, 1875.

[4] Kraushaar, "Entwick. d. Hyp. beim Säugethieren," *Zeitsch. f. wissen. Zoologie*, Bd. xli., 1885.

[5] Dohrn, "Studien zur Urgeschichte des Wirbelthierkorper's," *Mitt. der Zoo. Stat. zu Napel*, Bd. iii.

[6] Lothringer, "Untersuch. an der Hypophyse einiger Säugethiere und des Menschen," *Archiv f. mik. Anat.*, Bd. xxviii., 1886.

[7] Luschka, "Der Hirnanhang u. d. Steissdruse des Menschen." Berlin, 1860.

attracted the attention of observers. As mentioned in our previous paper, Peremeschko [1] laid considerable stress upon this relationship in his anatomical description of the pituitary. Lastly, a paper by Lothringer [2] in 1886 brings the normal histology of the pituitary up to date.

The Function of the Gland.—The *chemistry* of the gland appears to have been comparatively recently taken up by Flesch and Nencki, but with merely negative results. On the other hand, by the use of suitable *staining*, the former observer differentiated two classes of gland cells,[3] and Dostoiewsky [4] appears to have done the same. Lothringer, however, in Flesch's laboratory, added considerably to the knowledge of the staining reactions of these cells. He divided them into the two groups, chromophile and non-chromophile; the former are eosinophilous, and stain blue with indigo borax carmine, and give other characteristic reactions, whilst the latter do not stain with eosin. Both Flesch and Lothringer argue from these reactions that the gland is an active one. Numerous subsequent observations, including our own, fully confirm the various staining reactions; but we are not prepared to attach the same importance to them as others have done (see later).

A considerable advance in our knowledge of the function, and more especially of the relationship of the pituitary gland to the thyroid, was made about the same time by Rogowitch.[5] This observer, as mentioned in our previous paper, found marked changes in the hypophysis cerebri after extirpation of the thyroid in animals. These were followed by similar observations by Stieda,[6] Pisenti, and Viola,[7] and Hofmeister.[8] Still more recently Gley [9] gives us the weight increase of the hypophysis after thyreopriva. Thus, taking the average normal weight as ·02 gramme (rabbit), after thyreodectomy this was increased to ·03, ·05, and ·101; he speaks of this last weight as representing an "enormous hypertrophy."

By removing the hypophysis Horsley [10] sought to obtain a more accurate knowledge of the function of the gland. The experiments were, however, for the most part negative; an increase of the cortical excitability was, however, observed. Similar experiments have been made by Gley, but we are unaware of any definite result.[11]

[1] Peremeschko, "Ueber den Bau des Hirnanhanges," *Virchow's Archiv*, Bd. xxxviii., 1867.

[2] Lothringer, *loc. cit.*

[3] Fleseh, *Tageblatt der Versammlung. deut. Naturf. und Aerzte zu Magdeburg*, No. 4 (*ref.* Lothringer).

[4] Dostoiewsky, *Waldeyer's Archiv f. mik. Anat.*, 1886, H. 4.

[5] Rogowitch, *Ziegler's Beit.*, Bd. iv., ete.

[6] Stieda, *Ziegler's Beit.*, Bd. x.

[7] Pisenti and Viola, *Centralb. f. d. med. Wissen.*, 1890. Only a few experiments appear to have been made; one of the most marked changes appears to have been eystic dilatation (interfollienlar, aeeording to these observers).

[8] Hofmeister, *Fortschritte der Medicin*, 1892.

[9] Gley, *Archives de Phys. norm. et path.*, Oct. 1892.

[10] Horsley, "Brown Lectures, 1885," *Brit. Med. Journ.*, 1886, vol. i.

[11] Marinesco has recently given the results of extirpation of the hypophysis in cats, but they are negative (Soe. de. Biologie).

The Pathology of the Pituitary Body.—The experiments of Rogowitch appear to have been the cause of directing attention to a possible association between changes in the thyroid and hypophysis. Pisenti and Viola [1] described changes in the hypophysis in a case of struma fibrosum, which, they argue, might be due either to the same cause which produced the goitre or be the indication of a compensatory hypertrophy. In the preceding number of this *Journal* we described the enlargement of the hypophysis in myxœdema with athyrea, and drew attention to its changes in other cases of disease of the thyroid. Most recently Schönemann [2] set himself to seek whether the hypophysis showed anatomical changes, which might run parallel with changes in the thyroid. From an examination of the pituitary bodies and thyroids of 112 individuals, who died from various causes, he is led to believe in the close association of hypophysis and thyroid. As we ourselves are about to record the examination of 100 cases, we shall have frequent occasion to refer to his results, but we may here mention the very interesting condition which he observed in a case of thyreopriva. The case was that of a boy from whom Kocher removed the goitrous thyroid at 19. Cachexia thyreopriva ensued, and death took place at 25. Langhans [3] described the changes in the nerves of the case, whilst Schönemann undertook the examination of the pituitary. The weight of the gland was 1·59 grammes (that of our case of myxœdema was 1·21 grammes), and it appeared very large. As his average weight of the normal pituitary was ·6, corresponding with that of ours, he says that the case looks very much like one of compensatory hypertrophy. The microscopic characters of the gland appear precisely similar to those which obtained in our case; but from them he argues for a *goitrous degeneration* of the gland rather than for a compensatory hypertrophy. This argument is a fair one, and will equally apply to our case; he finds it difficult, however, to explain the enlargement in his case, unless that after the operation the patient returned to the former condition, which favoured the goitre; further, he instances the case of a cretin with a very large colloid goitre and a very small pituitary. We have, however, been fortunate enough to find that Nièpce [4] carefully records the post-mortem examination of 5 cases of cretinism, in every one of which the hypophysis was enlarged. His cases are as follows:—

Case 1. Male, æt. 22, cretin with large goitre, size of pituitary striking, protrudes from sella turcica, weighs 2·42 grammes.

Case 2. Male, æt. 17, cretin with goitre, pituitary body large, weighs 1·19 grammes.

Case 3. Female, æt. 23, thyroid normal, pituitary voluminous.

Case 4. Male, æt. 26, goitre, pituitary larger than normal.

Case 5. Male, æt. 32, no goitre, pituitary large, 1·19 grammes.

[1] *Loc. cit.*

[2] Schönemann, "Hypophysis und Thyroidea," *Virchow's Archiv*, Bd. cxxix., August 1892.

[3] *Virchow's Archiv*, Bd. cxxviii.

[4] Nièpce, "Goître et Crétinisme." Paris, 1851.

Nièpce is accredited with attributing cretinism to the enlargement of the hypophysis, just as Wenzel had done in the case of epilepsy: but we have not been able to find where he makes this statement. The fact, however, remains that in 5 cases of cretinism the pituitary body was enlarged; and that if these cases are added to Schönemann's case of cachexia thyreopriva, and to the cases of cretinism described by Bourneville and Bricon and Dolega, and our former case, the view gains support that some peculiar relationship exists between the cretinoid state and the condition of the thyroid and hypophysis.[1]

We have still insufficient data to decide the many points raised in the preceding pages. The reader will have, amongst other things, to gather from this short sketch of the various aspects of this interesting gland, as well as from subsequent evidence, whether it performs an active, though subordinate, physiological rôle; whether it is to be classed amongst the numerous "rests" with which we are acquainted—Gley's glands, spleniculi, suprarenal, hepatic, pancreatic rests, etc.; or whether it is a mere vestigial structure. On the other hand, it may be argued that in the cases of myxœdema, cachexia thyreopriva (in man), sporadic cretinism with athyrea, and this, too, in spite of the fact that the weight of the organ is double or even greater, that we are only dealing with fibroid degenerative changes, such as are common to all the glandular organs in these cachectic conditions. Here, again, more observation is required; but we may remind our readers that even Recklinghausen, amongst others, was not inclined to attribute any importance to the enlargement of the hypophysis in acromegaly. Few, we venture to think, with a knowledge of the cases of this enigmatical disease which have been published so far, would now hold similar views.

II. The Normal and Pathological Anatomy of the Pituitary Body.

The pituitary body is usually slightly broader than long. It is flattened from above down, and there is usually a slight depression upon the upper surface into which the peduncle is inserted; occasionally, however, there may be a considerable swelling in this situation. The diameter from side to side sometimes greatly exceeds the antero-posterior. In a few specimens we observed a very deeply trilobate outline, produced by the posterior lobe and bi-lobed anterior lobe. The major portion of the infundibulum usually passes into the posterior lobe, only a small portion in front spreading into the anterior lobe. In a considerable number of cases, however, the infundibulum is seen to enter the gland substance directly, and a median antero-posterior section shows that the infundibulum traverses the gland tissue to reach the

[1] We have not yet been able to examine Wenzel, "Ueber Cretinism," Vienna, 1812; and Aekermann, "Ueber die Kretinen," Gotha, 1790. Dr. Whitwell informs us that in a fatal case of sporadic cretinism which he lately examined there was no enlargement of the pituitary body.

posterior lobe, which is situated behind and below the anterior lobe, instead of, as is more usual, directly behind, or behind and above. In the adult, gland acini usually extend upwards for a little distance upon the anterior face of the peduncle, but occasionally, as in the last cited abnormality, they may ensheathe its lower end. This spreading of the gland tissue in the pia mater around the infundibulum has been described by Luschka, Müller, Lothringer, and others; in the young and in animals it may extend to the optic chiasma, and in one case in the adult (see p. 372) we found a small glandular collection in the angle between the infundibulum and the optic chiasma; in the monkey, also, we have observed gland tissue around the proximal end of the peduncle. A vertical antero-posterior section passing through the centre of the stalk and pituitary shows, when slightly magnified, that as a rule the small posterior cerebral portion is sharply marked off from the anterior glandular portion. We may speak of the part of the gland tissue, adjacent to the nervous, as the boundary zone, for it is more fibrous, contains the large vessels, is almost invariably cystic, and in it the hypophyseal fissure lies. Contrasting with this boundary zone, the rest of the anterior lobe is made up of closely-packed solid gland acini. In the same section it will often be seen that there is a very remarkable angular projection forward, or genu, formed by the anterior margin of the posterior lobe; an angular indentation is also sometimes seen on the posterior surface of the nervous lobe, and is due to the extension of the gland tissue posteriorly. Sections made horizontally through the pituitary body, and slightly magnified, show that the posterior lobe is, in a large number of cases, more or less completely embraced by the gland tissue; a remarkable button-like projection of the posterior lobe into the anterior will also sometimes be seen; it corresponds to the genu of the vertical section. In the tissue of the boundary zone a long slit may also sometimes be seen on each side of the button-like projection just mentioned; these slits are for the most part lined by a layer of gland-like cells, and they may be filled with colloid material; they have been termed the *hypophyseal fissures*. Peremeschko[1] regarded them as the continuation of the *infundibular cavity*, and stated that they might be lined by ciliated epithelium, but Lothringer looks upon them as the remains of the original buccal invagination. We have ourselves never seen, either in man or in the monkey, ciliated epithelium, and we are inclined to believe with Lothringer, from reasons to be stated hereafter, that they represent the duct portion of the gland; it may be mentioned that in the rabbit the cystic spaces are lined by ciliated epithelium, and that occasionally in man, as we shall have occasion to note, large ciliated cysts are observed. We have never, in man, observed the infundibular cavity; according to Luschka remains of it may be seen in the posterior lobe of the young, in the form of degenerated ciliated epithelium. In

[1] Kölliker believed that some of the cystic spaces were remains of the infundibular cavity.

the hydrocephalic, Langer[1] found an extension of the third ventricle into the pedicle for some distance; he also found in two cases small isolated spaces surrounded by epithelium.[2] In the monkey an irregular space which is not lined by a definite layer of epithelium, but which is surrounded by irregular groups of cells, may be seen in the posterior lobe.

The posterior lobe is for the most part composed of spindle-shaped cells; they sweep down from the pedicle, and then turn round in various directions, and give to the posterior lobe in section the wavy appearance characteristic of the fibromata, myomata, and spindle-celled sarcomata; indeed, numerous observers, amongst others Schwalbe,[3] Müller, and Lothringer, compare the structure of the infundibulum and posterior lobe to a spindle-celled sarcoma. Pigment cells are a striking feature of the posterior lobe. Cells resembling glia cells may also be seen, and the groups mentioned above may represent the cells which surrounded the infundibular cavity. Whilst the gland acini in the anterior lobe are for the most part solid, those in the boundary zone, as previously mentioned, are cystic and contain colloid; the hypophyseal fissures in this zone may, or may not, be well marked. The gland acini are closely packed together, the interspaces being occupied by an extensive capillary mesh work; the cells are usually small and well defined, and we have not been able to find any of the undifferentiated cell masses which Schönemann regards as normal. Stained with logwood and eosin, eosinophilous and cyanophilous cells may usually be made out; but we have noticed no constant difference in the size of the cells which yield these reactions.[4] Numerous vessels come down in the anterior pia matral covering of the infundibulum, and many of them appear to pass into the boundary zone as far as the genu, where some proceed forwards into the anterior lobe, and a few backwards, surrounded by connective tissue, into the posterior lobe. It is thus at the genu, or the button-like process, that the union between anterior and posterior lobes appears to us to be most marked. In some of the vessels, lumps of colloid material may be seen; extra-alveolar colloid is also seen in small quantity, but we have never met with the large inter-alveolar cystic clefts filled with colloid described by Pisenti and Viola.

The following are the more striking deviations which we noted in a hundred pituitary bodies, removed from subjects who had died of various diseases, but in which there was no noted change in the thyroid; about one-half the number were taken from insane cases. We found a great uniformity of structure throughout the cases, the alveoli were closely

[1] Langer, "Ueber cystische Tumoren im Bereiche des Infundibulum cerebri," *Zeitsch. f. Heilk.*, March 1892.

[2] See also Flesch, "Anat. Untersuch. eines mikroceph. Knaben." "Festschr. (of the 300th anniversary) der Julius, Max. Univ., Wurtzburg," Bd. ii. Petit, "Condition of Hypophysis in the Hydrocephalic," 1718. Von Stosch, "Degeneration of Pituitary in Hydrocephalus," *Woch. f. d. ges. Heilk.* Berlin, 1833.

[3] Schwalbe, "Lehrbuch der Neurologie."

[4] Good differential effects have been obtained by us with Biondi's stain.

packed, and the cells small, staining deeply with logwood. In a few cases, in which the alveoli were broader and more loosely arranged, the cells were larger, and in these cases large and small cells with intermediate sizes could readily be distinguished. In the boundary zone we were often struck by the more intense staining reaction of the alveoli, and in three cases typical small-branched *adenomata* were found in this zone and at the foot of the peduncle. The *adenomata* were cyanophilous, the nuclei large, and in the centre of the alveoli the cells were often arranged concentrically, and there were in addition undifferentiated multinucleated masses of protoplasm; they contrasted markedly with the surrounding gland tissue. It is from their presence and the difference of staining reaction in the boundary zone, as well as from the presence of the cystic spaces and hypophyseal fissures, that we believe that the duct portion of the gland is represented in the boundary zone. The variation in size of the hypophysis is almost invariably due to the glandular portion; in some cases the posterior lobe was scarcely represented. The cysts in the boundary zone in many cases reached visible proportions; we encountered a small cyst at the foot of the peduncle; in the colloid material, large uni- and multinucleated, clear, and in some cases opaque, cells were found. In a small proportion of cases the connective tissue covering the posterior lobe was rich in young fat cells; and, as regards the posterior lobe itself, the number and shape of its cells varied very greatly: in one case the section looked exceedingly like that presented by nerve substance, in other cases the cells were very numerous, and either spindle-shaped or oval; in a few, a myxomatous appearance was seen; long rigid fibrillæ, apparently cell processes, were often seen. The vascularity of the pituitary body varied, and this, as we shall see, depended largely upon the cause of death; but in a few cases there was an almost nævoid condition. In only three cases could fibrosis be said to be marked. Lothringer, in his analysis of 112 cases, looked upon pituitary bodies as abnormal when the chromophile cells predominated; and with associated, vascular, connective tissue, and colloid cystic changes, he regarded them as furnishing a condition equivalent to the goitrous state. But much more evidence is needed to show that chromophile cells and increased colloid formation represent degeneration, and may not mean increased activity; our view, however, will be modified according as we regard the pituitary body in the light of a *vestigial*, *accessory*, or *active* secretory gland.

Lothringer, in his examination of the hypophysis of the lower animals, found that its *weight* bore no relation to that of the brain; it was rather in proportion to the body generally. Schönemann gives the average between 20 and 30 years as ·63 gramme, and says that the weight then appears to diminish, so that at 50 it is about ·6 gramme, but that in goitrous individuals the weight appears to increase with age, or, in other words, that it increases

with the increase of the goitrous state. In our previous paper we gave figures of the average weight as stated by several authorities. We also recorded that which we had ourselves obtained from 50 female lunatics; this was appreciably higher than any of the others mentioned, being ·6 gramme. Our lowest weight, ·384, differed little from that noted by others, but our highest, of ·896, was nearly ·3 gramme above the highest elsewhere recorded. We made the remark at the time, that this difference might be "owing to the fact that the glands were obtained from the insane."

We are now able to give the figures obtained from 50 male lunatics. The average weight is ·453 gramme, with the highest and lowest respectively of ·712 and ·130 gramme. In these cases the ages varied from 22 to 78. The weights, therefore, from the male are smaller than those from the female; once the weight only reached ·1302, and once only did it reach as high as ·712 gramme. From these figures it would at first sight appear that the hypophysis in the female is, as a rule, of greater size than that in the male. Although to some extent we believe this to be true, yet we think that the difference in size here noted may, in part, be accounted for in another way. We will, however, first make a few remarks on the subjects from which our hypophyses cerebri were obtained.

We would note, with Lothringer, that *no relation appears to exist between the pituitary and brain weight*, for in some cases where the brain was especially small, the pituitary was above the average, and *vice versa*. Thus, in the male, the largest pituitary was with a brain weighing 46½ oz., whereas one of only half this size existed with a brain of 56¼ oz. Again, a brain of 37 oz. existed with a pituitary of ·453 gramme. In the female the same remarks hold good; the largest pituitary, of ·896 gramme, was in one case present with a brain weighing 44 oz., in another 34¼ oz.; and a pituitary of ·648 gramme was present with a brain of 46 and one of 37 oz.

In the same way, we believe there is no relation whatever either to the form or the duration of the insanity, although it may be said that a small pituitary is more often found with insanity of long duration. The pituitary of ·13 gramme was in a person of 58 years of age, with dementia of 34 years' standing. Other cases of dementia of about equal age, and where the insanity had lasted many years, had pituitaries that were above the average in size and weight. The number of epileptics of which we examined the pituitary bodies is very small; but, so far as they go, they are rather below the average than otherwise.

There is also no relation apparent in these cases between the size of the pituitary body, either to the general nutrition or to the age. But we believe a relationship exists to some extent between the size of the hypophysis and the mode of death. It is noticeable that the majority of the large pituitary bodies—that is to say, those above the average in weight and size—were found in persons who had died rapidly from acute inflammatory diseases, such as pneumonia, whereas those below

the average were often associated with death from phthisis and cardiac disease, or the exhaustion of insanity. Many of the hypophyses were from patients who died of complications following influenza, and under these circumstances there was found, post-mortem, a very marked congestion of the brain and membranes.[1] It is reasonable to suppose that this engorgement also affected the vessels in such a vascular organ as the hypophysis; sections, moreover, readily revealed the congestion.

Absence of the Hypophysis. — We have shown that the size of the pituitary body varies very greatly, one weighing ·13 gramme, and being about the size of a small pea. Absence of the pituitary appears to be extremely rare;[2] one of us, however, in an examination of over 150 brains, met with a case in which no trace of the organ could be found in the pituitary fossa. The fossa was occupied by a little loose connective tissue, and appeared a *little larger than normal*, especially as regards its depth. There was considerable emaciation of the patient, but the brain weighed 47 oz. Death was due to phthisis and diarrhœa.

The Pituitary Duct. — We have already given the evidence of the presence of a duct portion in the pituitary; we are, however, unaware of any epithelial connection between the pituitary and the pharynx in the adult having been described. Luschka mentions a case of miscarriage with spina bifida, in which the pituitary was prolonged into the sphenoid, and there existed an invagination of the mucous membrane upon the opposite side. Landzort[3] describes a prolongation of the dura mater through the sphenoid to the opposite side.

Fatty and Calcareous Degeneration of the Pituitary.—Although in a few cases we observed cloudy swelling in the cells, we never met with the fatty degeneration described by Virchow[4] in old people; we have also not observed a marked case of calcareous degeneration; an example however, of calcareous tumour, described by Krauss, will be found under "Tumours." Concretions have also been described by Vicq d'Azyr and Bichat (*ref.* Rayer, *see* Bibliography).

III. The Tumours of the Hypophysis Cerebri.

That tumours of the hypophysis cerebri and infundibulum are rare, one can readily convince oneself by examining the periodical literature of the last ten years, as well as the recent special literature on brain tumours.[5] We have, however, thought it consistent with the scope of this paper to find

[1] Cecil Beadles, "Post-mortem Appearances of the Brain in Influenza Patients," *Lancet*, 1892, vol. i.

[2] Absence of the hypophysis is not referred to in any of the 3000 odd autopsies recorded at Colney Hatch, but a case might easily have been overlooked.

[3] Henle's "Jahresb. f. 1868," p. 86.

[4] Virchow, "Untersuch. u. d. Entwick. des Schädelgrundes." Berlin, 1857.

[5] Starr, "Tumours of the Brain in Childhood, their Variety and Situation," *Med. News*, Phila., 1889. Oppenheim, *Archiv f. Psych.*, Bd. xxi. and xxii. Byrom Bramwell, "Intracranial Tumours," 1888. Bernhardt, "Beiträge z. Symptomatolgie u. Diagnostik der Gehirngeschwülste." Berlin, 1881.

out what are the grosser pathological lesions to which the pituitary is subject. It is evident that a knowledge of the neoplasmata of the pituitary may help us to strengthen comparisons between that body and the thyroid, and, indeed, it will be seen that there is a very striking similarity between the growths of both organs; thus, hypertrophies and cystic, colloid, or serous tumours predominate over all other forms; occasionally there is a dermoid or ciliated tumour, but these again are observed in connection with the thyroid or the remains of its duct. We have thought it worth while to give a brief summary of the chief symptoms which have been observed.

To the list of tumours of the infundibulum we are able to add the microscopic descriptions of cases of small growths. Whilst an analysis of the 3000 autopsy reports at Colney Hatch Lunatic Asylum (1868–1892) have furnished us with 6 cases of tumour of the hypophysis, which, considering that the total number of intracranial growths (excluding simple cysts of the brain and membranes, abscesses, aneurisms) in the whole 3000 cases is only 20, shows that of tumours, accompanied with insanity, those originating in the hypophysis form a large percentage. We are able to give the very striking description of a case of acromegaly, with cystic hypophysis; the autopsy took place in 1884, and therefore at a time when this disease had not attained recognition. It serves to swell the increasing number of cases of acromegaly associated with changes in the pituitary,[1] and with these to greatly weaken the view of the merely vestigial nature of the glandular portion of the hypophysis.

The tumours of the pituitary region may be divided into (1) acute and chronic infective tumours, such as abscesses and granulomata; (2) hæmatomata; (3) tumours of the infundibulum and posterior lobe; (4) tumours of the membranes surrounding the hypophysis, such as the lipomata; (5) the glandular neoplasmata; (6) teratomata.[2] Only the last two groups are those with which we are more especially concerned:—

Group I.—Acute and Chronic Infective Tumours.

Case 1.—*Tubercular-like Granuloma of the Anterior Lobe.*

Patient, 11,354, female, æt. 57, died March 1892, in Colney Hatch, with pneumonia and paralysis. Duration of insanity, three months; form of insanity, melancholia with delusions.

[1] In going over the descriptions of recent cases of acromegaly one certainly gains the impression that in the vast majority of them there is enlargement of the hypophysis. We, however, are unable at present to draw up a table of these cases, as the actual autopsies are very few; the tumours in very many instances being diagnosed from the eye symptoms, and as the enlargement need not produce any eye symptoms it is very probable that a large number of cases will remain undiagnosable till death.

[2] Sömmering (Baillie, "Anat. des krankhaften Baues") mentions a case of echinococcus cyst in hypophysis (ref. Breitner).

Present state.—Slight absence of facial folds on left side, protrusion of tongue to the right side. Complete amaurosis of left eye, which was kept partially closed, whilst the eyeball was turned outwards. Patient stated that she lost the sight of her eye from "neuralgia" two years ago. No history of syphilis.

Post-mortem.—Pleuritic adhesions and pneumonic consolidation of both lungs, no trace of tubercle in them or in the other viscera.

Head.—Calvaria and dura mater thickened; pia-arachnoid membrane only slightly thickened, and showing no trace of previous inflammatory lesions. Considerable amount of fluid within the skull. Brain small, 40 oz. Deficiency of brain substance on the under surface of the right temporo-sphenoidal lobe, whilst more anteriorly brain substance wanting, thickened pia-arachnoid separating the lateral ventricle from the exterior. Ventricles dilated with fluid. There was a hæmorrhagic softening, half an inch in diameter of recent date, situated in the left lenticular nucleus at the level of the anterior edge of the optic commissure; and another of still older date and smaller, situated on the right side, but a little further back. In the medulla oblongata was a small hæmorrhage internal to the olivary nucleus on the left side. The brain substance was considerably harder than natural, and the vessels within the brain had thickened walls and stood out prominently on the cut surface.

The pituitary body separated on removing the brain from the skull. It did not project above the level of the clinoid processes, but it completely filled the pituitary fossa. It was removed with some difficulty, for it was firmly adherent to the sphenoid bone on the right side; and on cutting through here, the tissue appeared of cartilaginous hardness; to the sight the cut surface might have been dense fibrous tissue or fibro-cartilage. The bone was quite healthy. The pituitary was of fair size, and weighed ·645 gramme. About one-third of the right half of the anterior lobe was composed of the tissue mentioned above.

On section the anterior lobe was found to be the seat of an extensive necrosis. Small round cells, proliferating small deeply-staining gland cells, and giant cells, surrounded the necrotic area, and gave the appearance common to that of the tubercular granuloma. In one place there was a considerable amount of dense hyaline connective tissue, in which were scattered collections of small round cells.

The case admits of the surmise that some of the optic troubles had been caused by a previous more pronounced granulomatous process, which had since healed, leaving the dense cartilaginous tissue previously referred to.

For recorded cases of granulomata and abscesses, Group I., and Hæmatomata, Group II., see Literature (*a*) and (*b*).

Group III.—Tumours of the Infundibulum and Posterior Lobe.

To this class we are able to add two cases.

Case 1.—*A Cellular Growth in the Infundibulum* (Plate XXI., Fig. 1).

Female, No. 9884, æt. 71, died in Colney Hatch, having been a lunatic 4 years. On admission deluded, ideas confused, with loss of memory. Nutrition fair. Complexion florid; hair scanty and turning grey; right hearing distance, two inches. Suffered severely from headache when young. Whilst in the asylum the delusions and loss of memory increased, slight dementia. On March 27, 1892, became paralysed on left side, and died from pneumonia on April 4.

Post-mortem. — Thorax. — Slight pneumonic consolidation of left lung; atheroma of great vessels; heart dilated and fatty.

Abdomen.—Kidneys were both enlarged, congested and hard, and somewhat granular on the surface. The right contained several round pale fibrotic areas. Spleen large and soft. Liver large, firm, fatty and fibrotic in places with pale areas in other parts. Weight ·64 oz., gall-bladder distended, and contained a very large number of yellow gall stones.

Brain.—Well-developed, weight 45½ oz. Pia-arachnoid much thickened. A large amount of fluid was present. There was dilatation of the lateral ventricles, more especially of the right. Vessels of ependyma were engorged, and vessels at base atheromatous. Brain substance firm; no hæmorrhage present. A small tumour existed at the base of the brain in the situation of the pituitary body, resting upon it and entirely outside the pituitary fossa. The tumour was the size of a medium-sized pea, of roundish form, firm, and appeared to be an "accessory pituitary body." The pituitary was in its usual position, and of about normal size and appearance, its weight being ·842 gramme, and it was quite independent of the tumour except for a slender connection passing up to the infundibulum of the brain, from which the accessory body appeared to take origin.

Fig. 1.

Thyroid body.—This was of normal colour and appearance. There was, however, a very narrow isthmus; several small hard nodules could be felt in the lobes, and there were a few small accessory processes of thyroid tissue passing from it. Weight of the thyroid gland was 300 grains.

Histology.—After embedding in celloidin, vertical sections were made through the base of the brain, the infundibulum with accessory body and the pituitary (the position of the latter having been restored); sections were stained with logwood, and with aniline blue-black. They show that, close above the hypophysis, the infundibulum swells into the small tumour figured. The growth is ¼ in. in diameter, and projects posteriorly. It is composed of large polygonal nucleated cells, larger than those met with in the anterior lobe; a few cells are, however, multinucleated, whilst in others the nucleus does not stain (Plate XXI., Fig. 2); a definite acinar grouping of the cells is only slightly apparent at the periphery, but the numerous capillaries tend to produce a certain amount of lobulation. Scattered amongst these cells are numerous spindle-shaped cells, similar to those usually seen in the infundibulum. Posteriorly, the tumour is covered by the thinned pia mater, whilst anteriorly the pia mater contains a few atrophied gland tubes and vessels; the tubes represent the upward continuation of the anterior lobe upon the infundibulum, and this prolongation serves to attach the accessory body to the hypophysis. Above the growth the infundibulum is composed of connective tissue and vessels. The anterior lobe of the pituitary consists of solid epithelial acini; the cells are slightly larger than normal, staining somewhat faintly. In the boundary zone there is considerable cystic dilatation and colloid formation, and the gland cells, as a whole, stain more deeply than elsewhere. The vessels are numerous. The demarcation between

the lobes is not well marked, for there exists a considerable infiltration of the gland cells into the posterior lobe. The cells of this infiltration closely resemble those in the tumour. The posterior lobe is composed of the characteristic spindle cells, which group themselves into definite bundles; there are numerous pigment cells. In the pia mater of the upper part of the pituitary there are numerous very large mulberry-shaped and stratified corpora amylacea.

Two views may be held concerning the nature of the above growth. We are more in favour of that which assigns to it a glandular origin, the size and grouping of the cells leading us to this conclusion. On the other hand, there appears no transition of the anterior gland acini into the accessory mass; many of the cells and their nuclei stain faintly, and this is a character of the cell groups sometimes met with in the infundibulum (see *ante*).

Case 2.—*Slight General Enlargement of the Infundibulum.*

We are indebted to Dr. P. R. Dodwell for the specimen and following notes:—

"A girl, æt. 16, had suffered from phthisis since 1891, and died Nov. 6, 1892, with no further symptoms.

"*Post-mortem.*—Both lungs presented caseous consolidation with excavation. Heart. — On the mitral valve were small red granulations, due to acute endocarditis. Kidneys slightly rough on surface, with adherent capsules. Spleen rough. There were some submucous patches of caseation in the appendix vermiformis. Thyroid body appeared quite healthy; there was a small well-marked pyramid attached to the right lobe. Brain appeared perfectly healthy in every respect to the naked eye. There was distinct fulness of the infundibulum towards its free anterior end; it was not of the nature of a definite tumour, as was seen in the other case, but was a simple bulging. It was soft, but felt solid to the finger. The pituitary body was separated on removing the brain from the skull; it was of average size, and weighed ·324 gramme."

A section through the enlargement showed that this was due to very definite collections of spindle cells; the appearance being highly suggestive of a spindle-celled sarcoma. Along the anterior surface of the infundibulum there is a prolongation of gland tubes, and these form in the angle between peduncle and optic chiasma a small but very definite *gland growth.* The cells of the anterior lobe are both of the small and large variety.

Langer[1] has recently described two cystic tumours which he believes are of infundibular origin. In one case there was a cystic growth between the corpora albicantia, infundibulum and optic chiasma; it was bound to the tuber cinereum and root of the infundibulum, and compressed the pituitary below it. In the other case there was a papillomatous cyst (hazel-nut size), containing serous fluid. The author believes that both sprung from the infundibular canal, for the nervous tissue of the infundibulum passed directly into the cyst walls, whilst the

[1] *Loc. cit.*

glandular portion stopped short. But from our knowledge of the oftentimes wide distribution of the gland acini, it would be difficult to eliminate these entirely.

Both were lunacy cases, and the symptoms before death were: headache, marked second and third nerve disturbances, at first more pronounced in one eye; stupidity, etc. See Literature (*c*).

Group IV.—See Literature (*d*).

Group V.—The Hypertrophies, Adenomata, Cystomata, and Carcinomata of the Glandular Hypophysis Cerebri.

The hypertrophies, adenomata and carcinomata, merge into one another, and the terms express little more than glandular overgrowth reaching striking proportions. The cystic glandular tumours include simple serous and colloid cysts, papillomatous cysts, ciliated and stratified cysts; all these cysts are compatible with what we know of the anatomy and development of the glandular hypophysis. The more complex cystic formations are described under the teratomata.

The following six cases are taken from the analysis of 3000 autopsies in Colney Hatch Asylum:—

Case 1.—*Enlargement of Hypophysis Cerebri.*

7127, male; admitted June 1877, suffering from acute mania. He was subject to epilepsy. This attack had been a week in duration, but he had had a previous attack. Delusions multiform. Further history is as follows:—March 1878, very childish and incoherent, gesticulates. February 1879, slovenly, but improved mentally and bodily. April 1880, good bodily health, but incoherent and deluded. January 1882, disposed to violence. December 1883, feeble in mind and body. Died January 1886 from pleuro-pneumonia and exhaustion of dementia; æt. 62.

Post-mortem.—Body fat and well developed. Head.—Calvaria thick, pia-arachnoid thickened, and slightly opaque. Brain well developed and of normal consistency and appearance throughout. Whilst removing the brain the pituitary body was seen to be enlarged to about the size of a walnut; it was adherent to the pituitary fossa. Beyond the pneumonic consolidation of the right lung, there was nothing further to note. The condition of the thyroid was not stated, and was therefore probably not enlarged. It is worthy of note that this large tumour apparently gave rise to no marked eye symptoms.

Case 2.—*Cyst of Hypophysis Cerebri.*

5070, female; admitted January 1873, suffering from mania, with delusions. Attack of six months' duration; she was suicidal, and dangerous to others. On admission, thin and pale; chatty; died one week afterwards from bronchitis; æt. 63.

Post-mortem.—Body fairly nourished for the time of life. Height, 5 ft. Head.—Calvaria abnormally thick, being over $\frac{1}{2}$ inch anteriorly, and nearly $\frac{1}{2}$ inch posteriorly; it was soft and spongy. Dura mater thickened. Pia-arachnoid congested, with fluid in meshes and Pacchionian bodies rather large. Brain substance firm and of good consistence, ventricles dilated and contained fluid. Weight of brain, $51\frac{3}{4}$ oz. The pituitary body was converted into a cyst. No marked pathological condition of other organs, except the bronchitic state of the lungs and some atheroma of vessels.

CASE 3.—*Cystic Tumour of Hypophysis Cerebri.*

8943, female; admitted January 1884, suffering from mania. Present attack of 3 weeks' duration, but had a former attack. On admission, pale and weak; œdema of feet and legs; face puffy and waxy. *Quite blind;* reads and writes by the blind alphabet. Had scarlet fever when 3 years of age, and had been blind since she was 5 years. Continued with alternate attacks of excitement and melancholia till March 1885, when she died. A few days previous to her death she had become semi-comatose, and died comatose; æt. 35.

Post-mortem.—Body was very pale, waxy looking, well nourished; no hair on pubes or in axilla. Calvaria was thin and pale; membranes of brain about normal in appearance. The frontal lobes of the cerebrum were softened, and readily broke down under pressure; central white portion somewhat toughened; the whole brain anæmic. Lateral ventricles not dilated, and no excess of fluid present. Corpora striata softened. At the base of the brain, resting upon the sella turcica, and extending backwards and pressing upon the pons Varolii, was a cyst as large as a walnut. This also pressed upon the optic tracts and the optic commissure, and filled up the whole space between the temporo-sphenoidal lobes of the cerebrum. A portion of the walls of the cyst was partially "ossified," and firmly adherent to the posterior-clinoid processes. It contained a greenish-yellow grumous matter, and weighed probably nearly an ounce. No pituitary body was observed. The heart was small and very flabby, quite empty in all its cavities, and there was some slight roughening of the mitral and aortic valves. Lungs.—Slight congestion at base. Liver small and rather congested. The right kidney very small, but appeared healthy, as did the left. Spleen very large and bloodless. Uterus undeveloped. (The thyroid gland was not examined; there was evidently no tumour in this region, as such would have been noticed.)

CASE 4.—*Case of Acromegaly with Cystic Hypophysis Cerebri.*

The following lucid account is taken from the notes, and evidently describes a typical case of acromegaly:—

8948, female; admitted February 1884, suffering from numerous delusions. She was single, and had been a washerwoman. On the day of admission her health was much impaired; very stout, weight 14 st. 2 lbs. A hugely bony woman, with a lowly organised head, having large zygomatic processes, prominent frontal sinuses, and a receding forehead; her ears and jaw immense for a woman, her hands spade-like, and her feet enormous; had the frame of a very large gross male. She is pale and flabby, and the leg muscles appear atrophied, the ends of the bones giving an exaggerated nodosity to the limbs; feet were œdematous, and at first sight there appeared to be general œdema resembling a case of myxœdema; a history which was apparently trustworthy of having large hands and feet, etc., only within last 16 years. There was a puffiness over the right clavicle. Feeble in gait, and could not walk alone owing to paresis of lower limbs. Cardiac disease, with mitral murmur; gentle and mild in manner; could write and read; slept well at night, and had a drowsy, heavy, lethargic look, and complained of headache; takes her food badly. Had formication and spectral illusions and aural hallucinations.

February 17th.—Sleepy and drowsy by day, and sleepless at night till after 2 A.M.; refuses medicine. Complains of pain in the knee.

February 20th.—Attacks of vomiting, with diarrhœa and prostration; is very thirsty, and has a rapid pulse.

February 23rd.—Diarrhœa has ceased, and she is much better, but is still feeble and pale.

February 28th.—Raving and noisy in the ward, and using filthy expressions.

March 13th.—Quiet again; subject to syncopic attacks.

February 29th.—Depressed and dull mentally, heavy and drowsy, often asleep, but does much needlework when awake.

July 16th.—Has remained in the same condition, often asleep for hours in the daytime. Is not deluded. Complains of rheumatic pains, and is subject to aural catarrh. Appetite good.

July 1st, 1885.—There has been no change; weak-minded, but without delusions. Occasionally liable to hæmorrhage from stomach and rectum.

September 25th.—Yesterday was in usual health. To-day has been vomiting blood of a black coffee-ground nature with large congealed clot. Towards evening respiration became frequent, little air entering chest, and pulse feeble; she remained conscious, but did not speak. Death took place the following day from exhaustion after hæmatemesis; æt. 40.

Post-mortem.—Body well nourished, with an enormous bony skeleton, "hands and feet being very gross"; about an inch of coarse fat on the abdomen, not greasy, but clean dropsical fat. No pitting on pressure of any part of the body.

Head.—Calvaria[1] thin, and almost papery in places; enormous frontal sinuses almost an inch across above eyebrows, and continued into the forehead and towards vertex. Dura adherent, pia-arachnoid rather congested, but stripped readily. The brain was with difficulty removed from the sella turcica, there being a cystic continuation adherent all round; the bone had been absorbed so as to leave a cavity the size of a small hen's egg; in removing the cyst, which came off with the brain, semi-organised grumous matter ran out. The tumour had pushed the optic commissure forwards, and had absorbed the floor of the third ventricle, and occupied the place of infundibulum, pituitary body, locus perforatus anticus on both sides, and encroached on both olfactory nerves. The arteries at the base of the brain were healthy in appearance, as also those internally. Both lateral ventricles were dilated, beyond which nothing abnormal was observed within the brain.

Thorax.—Lungs, both slightly congested, the left totally adherent to the chest wall, and surrounded by false membrane about $\frac{1}{8}$ inch thick, of old date. Heart flabby, large, with a gelatinous-looking muscle. Mitral valve diseased, with thickened cords and free fibrinous bodies of a mucoid consistence attached to its margin. Aorta healthy. The apex of the heart was adherent to the pericardium.

Abdomen.—Liver tough, fibrous, flabby appearance, but not larger than normal; greatly dilated venous canals throughout, which could be followed and traced with ease. Kidneys both weighed over 12 oz. each, large, reddish, owing to being full of blood; capsules not adherent. Spleen large, not tough, weight $20\frac{1}{2}$ oz. Stomach greatly distended with gas and fluid contents; it contained between one and two pints of dark coffee-ground blood. No ulcer or lesion found in any vessel, but a general capillary congestion of the mucous membrane. The large bowel was in places much distended. Nothing abnormal noticed about uterus, ovaries, or bladder.

Thyroid.—The thyroid gland was increased in size; weighs about 3 oz. This appeared due to a simple hypertrophy.

Case 5.—*Tumour of Hypophysis Cerebri* (*probably secondary*).

9289, female; was admitted September 4th, 1885. She is quite deaf, but readily answers written questions. She is full of delusions. Single; had been a domestic servant. In 1883 she was in Hoxton House; since her discharge she had been "strange." On admission she was thin, weight 8 st. 4 lb.; very deaf, requiring written questions put to her; was able to read and write. Deluded as to people following her and talking about her.

[1] A section passing through the frontal sinuses has been preserved, and we have been enabled to confirm the enormous enlargement of these sinuses.

September 11th.—Health fair, sits quietly in the ward, unemployed, mutters about the "quiet and silent persecutions." Clean and neat in appearance.

March 29th, 1887.—Has had a slight rheumatic attack, followed by pericarditis with effusion, and is still in a weak condition.

June 1st.—There is a tumour in the right breast, which was first noticed in March last; it is small, free, and non-adherent, and is not painful.

August 30th.—Weakness in legs, and confined to bed with pains in legs and back, slight rise of temperature.

September 9th.—Has been about a little, but now has pain in thighs. There is a zone of hyperæsthesia, which is not well defined, up to level of tenth dorsal vertebra. Strabismus, apparently reflex in origin, frequently comes on, accompanied with insomnia. Urine sometimes passed involuntarily. Died January 7th, 1888, from cancer of right breast and paraplegia. She had been confined to bed for some months, not being able to walk; great emaciation. She had a cancer of the right breast, which did not discharge; during the last few months a small open sore appeared around the nipple. The glands in the axilla were much enlarged; she remained very deaf; æt. 55.

Post-mortem.—Performed about 38 hours after death. Rigor mortis present. Body emaciated. Tumour in right breast, which had ulcerated through the skin.

Head.—Calvaria not thickened. Slight excess of fluid in the sub-arachnoid space. Convolutions of brain large; lateral ventricles dilated, and contained fluid. The pituitary fossa was occupied by a new growth, which was firmly adherent to the body of the sphenoid bone; white on section; consistence firm, with isolated softened patches. The growth involved the apex of left petrous bone, and almost the whole of the body of the sphenoid, pressing on the soft structures around.

Thorax.—Tumour in right breast did not completely involve pectoralis major; right axillary glands enlarged. There was a secondary deposit in the ninth rib of right side, and fourth rib of left side. The pleura of right side was affected, and firmly fixed to the sternum. Lungs somewhat collapsed. Heart small and atrophied.

Abdomen.—Liver large and fatty. Kidneys anæmic and pale. Spleen small and firm. Uterus small, and had several fibroid tumours, some extra-mural, others intra-mural.

Case 6.—*Cystic Tumour of Hypophysis Cerebri* (*probably dermoid*).

7680, male; admitted November 28th, 1878. Deluded, restless, and at times inclined to be violent. The attack was of three weeks' duration. His condition was said to be the result of intemperance; he fell on his head three weeks ago.

April 2nd, 1879.—Is considerably improved.

June 8th, 1880.—Remains in about the same condition.

February 27th, 1881.—Somewhat more impaired both mentally and bodily.

December 17th, 1881.—Died from maniacal exhaustion and cerebral tumour. Latterly the patient's sight had become much impaired, and he complained much of his head, and would frequently keep his hand pressed against it. Sometimes he would stagger in walking; æt. 62.

Post-mortem.—Body fairly nourished. Brain, weight 43 oz. Arachnoid slightly opaque, with a large collection of serous fluid in the sub-arachnoid space. Arteries of brain extremely atheromatous. Cerebral substance soft on section, presenting a worm-eaten appearance of small cavities in left hemisphere. Lateral ventricles enormously distended with clear fluid. At the base of the brain, within the circle of Willis, was a tumour of about the size

and shape of a pigeon's egg, and placed vertically. Its surface was irregularly nodulated, and its principal (and almost only) connections appeared to be with the pituitary body and the arachnoid. Very few vessels could be traced to the tumour. The right posterior communicating artery had to make a considerable detour to circumvent the obstacle. The tumour presented a glistening surface, and on section it was found to consist of a cyst wall of moderate thickness and soft, yellowish-white, cheese-like contents. This structure strongly resembled that of a sebaceous tumour, and on placing some of the contents under the microscope, numerous plates of cholesterine were found together with large rounded cells—in which no distinct nucleus could be observed—and granular matter. The tumour had evidently exerted considerable pressure on the structures surrounding it, especially upon the optic tracts.

Thoracic and Abdominal Organs.—Lungs very emphysematous, and their bases congested. Heart, weight $10\frac{1}{2}$ oz., apparently normal. Liver congested, weight 43 oz. Kidneys normal, right $5\frac{1}{2}$ oz., left 5 oz. The state of thyroid gland was not mentioned.

Two Cases of Large Tumour of the Hypophysis Cerebri.[1]

For the following two interesting cases we are indebted to our friend Dr. Ernest Wills, Assistant Medical Officer at Rainhill Asylum, and to Dr. Waddell of Manchester. As both cases will shortly be published in full, we simply append the following short notes:—

Dr. Ernest Will's Case.

The tumour occupied the interpeduncular space at the base of the brain, lying principally in a hollow between the left frontal lobe and the left crus cerebri. The olfactory nerves were flattened, and both optic tracts much atrophied, especially the left. Slight wasting of the pons medulla and right crus cerebri was noted. The tumour consisted of two parts, connected by a pedicle. The upper portion was soft and glistening and the size of a Tangerine orange, encapsuled, and divided into two unequal parts; a soft, flatter, darker basal portion, which was cystic, and a more prominent, hard, yellowish, spongiform part, size of a marble, gritty, seated on the right anterior segment. The latter was continuous with the growth in the pituitary fossa and infundibulum. The lower portion of the tumour occupied the sella turcica; its anterior half was very soft, and was found to be a cyst containing a viscous, greenish-yellow glistening fluid; the posterior was rough spongioid, and the seat of a recent hæmorrhage.

Microscopical examination of the solid portion of the tumour exhibited a structure resembling that of the thyroid body, viz. small cysts of various sizes, lined by columnar epithelium, and containing cells or a viscid substance. There were no signs of malignancy.

The sella turcica was much broadened, and its constituent bones were remarkably thin, the basilar portion being a mere lamina, and very brittle. The floor was pitted, in places, into cavities the size of a split pea, but there existed no communication with the buccal cavity.

There was no other feature of special interest, except that the skull was broad and low, the membranes were thickened, and the hands were broad and somewhat spade-like. No abnormality was noted about the thyroid region, but the gland was not specially examined.

[1] A pituitary tumour of great size and undoubtedly malignant, has lately been seen by one of us; it was found in a man, partially blind, who died in the Cancer Hospital during this year. The case will be published by Mr. Le Quesne.

The case was one of a man, æt. 26, who had sufferred from headache for 15 years,—these had become very severe the last 6 months,—and become demented. No fits. Left eye nearly blind; no reaction to light; he had external strabismus. Optic atrophy both sides. No paresis, but the patient staggered in walking. He became dull and comatose before death.

Dr. Waddell's Case.

The tumour was clearly defined and movable, solid, oblong in form, and measured nearly an inch in longest, and over half an inch in smallest, diameter. Flattened somewhat from above down. It was a simple hypertrophy of the anterior lobe, was highly vascular, and showed no characters of malignancy whatever.

Unfortunately the specimen was destroyed before it could be examined microscopically. The chief symptoms were, in order of occurrence:—Bi-temporal hemianopsia, periodic headache (frontal), unequal pupils; more frequent and more violent headache, accompanied by sudden rise of temperature and rapid pulse, with flushing of face; gradual failure of memory for recent or present events; transient hemiplegia (right), with aphasia, prostration, and gradual sinking; death from asthenia. The total duration of symptoms was about 2 years. There were no acromegaly symptoms present, and no mental symptoms, properly so called. A sister of the patient, whose death was very sudden and unexpected, had some brain trouble, symptomatised by violent and incurable hemiplegia.

LITERATURE OF CASES BEARING UPON THE PRECEDING CLASS OF TUMOURS.

(*a*) Group I.

Wagner, ... *Archiv d. Heilk.*, Bd. ii., 1861.—Tubercle of Pituitary, half-cherry size. Girl, æt. 13. Tubercle not present elsewhere. Protracted convulsions, loss of consciousness, and death in 12 hours.

Beck, ... *Ammon's Zeitsch. f. Ophthalmologie*, Bd. iv.—Tubercular Degeneration of the Pituitary as a cause of Diplopia and Strabismus.

Weigert, ... *Virchow's Archiv*, Bd. lxv.—Gumma (? Tubercular), hazel-nut size. Growth more upon one side, with pressure on optic nerve and eye symptoms.

Barbacci, ... *Lo Sperimentale*, 1891.—Gumma of the Pituitary.

Battiscombe, ... *Lancet*, 1888.—Abscess of Sella Turcica and Pituitary. Symptoms rapid—weakness, nausea, headache, photophobia, protrusion of eyeball, and death.

Harvey, ... *Dublin Quart. Journ. of Mde. Sc.*, 1855.—Abscess of Pituitary, with Caries of Temporal Bone. Optic nerve pressed upon. Sudden and complete amaurosis.

Heslop, ... *Dublin Quart. Journ. of Med. Sc.*, 1848.—Abscess of the Pituitary with Hypertrophy.

(*b*) Group II.—Hæmatomata.

Anders, ... *Journ. Nerv. and Ment. Diseases*, Jan. 1892.—Hæmorrhagic Tumour of the Pituitary Body

and Infundibulum in a case of Pernicious Anæmia. Female, æt. 34. After typhoid showed symptoms of giddiness, headache, nausea, slight loss of consciousness, delirium, and death.

EPPINGER, ... Hæmatoma in Posterior Lobe, walnut size.

BRODOWSKY, ... "Struma angioides." *Sitzungsb. der ärztl. Gesell. in Warschau Medycyna*, No. 25.

(*c*) GROUP III.

Langer brings forward the further following cases amongst others :—

MALACARNE, ... Meckel, "Handb. der Path. Anat.," 1812, Bd. i., p. 273. — Infundibulum as thick as a goose-quill (comp. Case 2), and surrounded by a small cyst.

RAYER, ... *Archiv. gén. de méd.*, 1823.—Infundibulum, 8–9 lines in diameter ; amaurosis, etc.

ROKITANSKY, ... "Handb. der Pathol. Anat.," 1856, Bd. ii., pp. 468 and 475.—Formation of a thick white-walled cyst in infundibulum, and mention of cysts with cauliflower growths usually situated upon the tuber cinereum (?glandular).

To these we may add, as probably derived from the posterior lobe :—

HOFFMANN, ... *Virchow's Archiv*, Bd. xxiv.—A large spindle-celled growth of the pituitary region, causing rapid symptoms in a child.

WHITWELL, ... *Journ. Mental Sc.*, vol. xxxv., p. 199.—Myxosarcomatous tumour of not very rapid growth.

v. GRAEFE, ... *Graefe's Archiv f. Ophthalmologie*, Bd. xii.—Gliosarcoma.

(*d*) GROUP IV.—LIPOMATA—TUMOURS OF THE MEMBRANES.

WEICHSELBAUM, ... Virchow's Archiv, Bd. lxxv.—A fatty tumour in the position of the posterior lobe. We believe that this tumour originated in the fatty tissue often present in the connective tissue covering the posterior lobe.

(*e*) GENERAL.

ABERCROMBIE, ... "Pathological and Practical Researches on Diseases of the Brain and Spinal Cord." Egg-sized tumour attached to an enlarged pituitary ; child.

ANDERSON, ... Vascular Tumour of Pituitary. *Brain*, vol. ix.

AUCHÉ, ... Glande pituitaire et ses maladies. Paris, 1873.

BACKER, ... Fibrose Geschwülst der Dura mater. *Schmidt's Jahrb.*, Bd. lxxiv.

BOWLBY, ... St. Bartholomew's Hospital Museum, Series xxx., No. 2446A. Epithelial cysts and bone. *Trans. Path. Soc. London*, 1885.

Breitner, ...	Adenoma (pigeon's egg). *Virchow's Archiv*, Bd. xciii.
Burrows, ...	*Lond. Med. Gaz.*, vol. 36, p. 485.
Chater, ...	On the Pituitary Gland. *Prov. Med. and Surg. Journ.* London, 1845.
Chevalier, ...	*Lond. Med. and Phys. Journ.*, 1827, p. 498.
Cunningham, ...	*Journ. of Anat. and Phys.*, July 1879. Hypertrophy.
Eisenlohr, ...	*Virchow's Archiv*, 1876, Bd. lxviii. Adenoma with hæmorrhage.
Engel, ...	Ueber den Hirnanhang u. dem Trichter. Diss., Wien, 1839. Pea-sized cyst at lower end of infundibulum.
Friedreich, ...	Beitr. f. Lehre von den Geschwülsten innerhalb der Schädelhöle. Wurzburg, 1853.
Gläser, ...	*Berlin. klin. Woch.*, 1883.
Goodhart, ...	*Trans. Path. Soc. London*, vol. xxxvi. Tumour in the baboon. Also *Trans. Path. Soc. London*, vol. xxv. Two tumours, probably glandular.
Greding, ...	Melancholico-maniacorum et epilepticorum quorumdam in ptochotropheo Waldhemionsi defunctorum sectiones. Leipsig, 1771. Gives cases of enlargement of hypophysis cerebri.
Habershon, ...	*Med. Times and Gazette*, 1864.
Hedlund, ...	Hypertrophie af glandula pituitaria och daraf berœnde blindhet. *Ars-Berätt om Svens. Läk. Sellsk. Arb.* Stockholm, 1833.
Heusser, ...	Ein Beitrag zur Casuistik der Hypophysistumoren. *Virchow's Archiv*, 1887, Bd. cx. An alveolar-like lympho-sarcoma of anterior lobe (? glandular).
Hippel, ...	Ein Beitrag zur Casuistik der Hypophysistumoren. *Virchow's Archiv*, 1891, Bd. cxxvi. A glandular tumour.
Ingermann, ...	Diss., Berne, 1889. A struma vasculosa, with gelatinous and cystic changes of stroma.
Kerr, ...	*Brit. Med. Journ.*, 1890. Walnut-sized cystic tumour.
Kerr and Major, . . .	Adenoma. *Lancet*, 1891, vol. i., p. 195.
Klebs, ...	*Vierteljahrssch. f. prak. Heilk.*, Bd. cxxv.
Krimer, ...	Seltene veranderungen des Hirnanhanges. *Jahrb. d. prakt. Heilk.* Berlin, 1821.
Lancereaux, ...	*Bull. Soc. Anat. de Paris*, 1859. Tumour.
Leber, ...	*Graefe's Archiv*, Bd. xiv.
Lebert, ...	Ueber Krebs u. d. mit Krebs verwechselten Geschwülste im Gehirn. u. seinem Hüllen. *Virchow's Archiv*, 1851, Bd. iii. Records of observations.
Leclerc, ...	*Rév. de Méd.*, 1887. Gland tumours, one case, probably secondary infection.
Legendre, ...	Cancer des nerfs moteurs oculaires communs et de la glande pit. *Bull. Soc. Anat. de Paris*, 1838.
Levy, ...	Ein Beitrag zur Casuistik der Hypophysistumoren. Diss., Heidelberg.
Loeb and Arnold, . . .	*Virchow's Archiv*, Bd. lvii. Adenoma (pigeon's egg).
Maier, ...	*Virchow's Archiv*, 1858, Bd. xiv. Walnut-sized tumour.

Mayet, ...	*Lyon méd.*, No. 15. Walnut-sized tumour.
Michel, ...	*Medico-Chir. Rev.*, 1862, vol. ii., p. 93. Pathology of the pituitary body. *Charleston Med. Journ. and Rev.*, 1860 (ref. *Med. Times and Gazette*, vol. ii., 1860).
Morgagni, ...	Mentions enlargement.
Mohr, ...	Mittheil. f. neuropath. Studien. *Schmidt's Jahrb.*, Bd. xxx.
Musée Dupuytren, . . .	One case of large hypertrophy, and models of two cystic tumours. *Bull. de la Faculté*, 1806 and 1817, tome v., p. 309.
W. Müller, ...	*Jenaische Zeitschr. f. Naturw.*, 1871. Cystic adenoma.
Nettleship, ...	Vascular Tumour of Pituitary body. *Ophthal. Soc. Trans.*, vol. iv. p. 285.
Nouridjan, ...	Cancer de la glande pituitaire. *Gaz. méd. de l'orient.* Const., 1878–80, tome xxii.
Ogle, ...	*Trans. Path. Soc. London*, vol. ix., p. 14.
Petrina, ...	Klin. Beitr. zur Localisation der Hirntumoren. *Vierteljahr. f. d. prakt. Heilk.*, Bd. cxxxiii. and cxxxiv. (? Sarcoma.)
Rath, ...	Beitrag zur Symptomatologie der Geschwülste der Hypophysis cerebri. *Graefe's Archiv*, Bd. xxxiv. Two cases, one glandular. Literature.
Rayer, ...	Obs. sur les maladies de l'appendice sus-sphénoidal du Cerveau. *Archiv. gén. de Méd.*, 1823. Gives 5 new cases, and refers to cases by Petit, Morgagni, Vicq. d'Azyr, Bichat, Baillie, Chaussier, and Rullier.
Ribbert, ...	Adenoma (walnut). *Virchow's Archiv*, 1890.
Roscioli, ...	*Neurolog. Centrlb.*, 1891. Nut-sized adeno-carcinoma.
Saundby, ...	*Brit. Med. Journ.*, 1888, vol. ii., p. 1224. Tumour.
Scott Ord, ...	*Edin. Med. and Surg. Journ.*, 1852, and *Glasgow Med. Journ.*, 1854. Four tumours.
Sibly, ...	*Brit. Med. Journ.*, 1888, vol. i., p. 134, and *Trans. Path. Soc. London*, vol. xxxix. Adenoma in ewe, blind for 2 years.
Taylor, ...	*Trans. Path. Soc. London*, vol. xxxv. Adenoma.
Thorburn, ...	*Lancet*, 1891, vol. ii., p. 1441. Tumour (Waddell's case).
Wagner, ...	*Archiv. d. Heilk.*, 1862. Cystic papillomatous (walnut-sized).
Ward, ...	*London Med. Repository*, 1823, vol. xx.
Weichselbaum, ...	Zu den Neubildungen der Hypophyse. *Virchow's Archiv*, Bd. lxxv.
Weigert, ...	*Virchow's Archiv*, Bd. lxv. Large adenoma.
Zenker, ...	*Virchow's Archiv*, Bd. xii. A very large cystic tumour; child. Cysts lined by stratified epithelium, serous fluid. Refers to Bonet (Boneti sepulchretum, Genevæ, 1679), who gives the case of a child with cystic tumour containing two pounds of fluid.

In addition to the above cases, the Museums of the Royal College of Surgeon's, St. Bartholomew's, Guy's, and London Hospitals, contain

between them 10 specimens, all of which are most probably glandular; all but 4 are, however, described in the preceding literature. No specimens could be found in the museums of University College, Charing Cross, King's College, Middlesex, St. Mary's, St. George's, St. Thomas', and Westminster. None are to be found in the Wakefield and Rainhill Asylums. In connection with our search through the museums, we desire to express our thanks to their Curators, and especially to Drs. Targett, Tonks, Willett, Rolleston, and Goodall.

Group VI.—Teratomata. Only a few cases have been recorded.

Beck, ...	Prager, *Zeit. f. Heilk.*, Heft 5, 6, and *Zeit. f. Heilk.*, 1883, Heft 4. Tumour (walnut-sized), and was a dermoid dentigerous cyst, with smaller cysts lined by ciliated epithelium; remains of the anterior lobe were present.
Sainsbury, ...	*Trans. Path. Soc. London*, 1886, p. 37. Tumour in region of pituitary, showing the structure of skin and subcutaneous tissue, but with no hair follicles nor sweat glands.
Hale White, ...	*Trans. Path. Soc. London*, 1885. A myoneuroma, composed of bundles of medullated nerve fibres and striated muscle fibres, connective tissue, fat cells, and what appeared to be a sympathetic ganglion. Dr. Hale White very kindly sent us sections of this tumour.

IV. Symptomatology.

A glandular organ like the pituitary body, which shows the unmistakable signs of activity, is always a source of danger, owing to its close proximity to the brain. On the other hand, the pituitary is deeply buried in the sella turcica, and partly shut down by dura mater. This buried position accounts for the fact that tumours which excavate the bone in the region of the sella turcica to the diameter of a walnut, or even, as in one of our cases, to that of a small hen's egg, may produce no apparent symptoms. In these cases the growth may extend into the ethmoidal cells and orbits. Unfortunately, however, a very large number of the tumours grow into the cranial cavity, press forwards towards the optic chiasma, and still more, laterally towards the third nerve; they press upwards against the non-resisting floor of the third ventricle, produce its atrophy, and they may even project into the ventricles. Some of the more rapidly infiltrating growths spread over wider areas, and may involve many of the other cranial nerves. Enlargement is usually more pronounced on one side. With regard to the symptoms, much will depend therefore upon the direction of the extension of the growth; but a very great deal also depends, as one would expect, upon the rapidity of growth. Thus a rapidly-formed tumour, the size of a small filbert, may give rise to acute symptoms and death;

whilst tumours the size of a walnut, and when projecting, may remain undiagnosed. The tumours giving rise to acute symptoms are abscesses, granulomata, hæmatomata, and rapidly-growing vascular tumours. The symptoms in these cases may be summed up as headache, nausea, giddiness, convulsions, loss of consciousness, photophobia, or sudden amaurosis, protrusion of eyeball, delirium, coma.

In chronic cases the duration of symptoms varies very greatly—from years to months; they are progressive. Headache is always a marked and early symptom, it is sometimes frontal; nausea and disturbances of digestion are also very common (pointed out by Lebert). Early onset of eye symptoms, usually first on one side, then spreading to the other; amblyopia, hemianopia, complete or intermittent amaurosis, strabismus, ptosis, exophthalmos, at first negative ophthalmoscopic signs, later choke disc, inequality of pupils. Drowsiness, often marked. Loss of memory and general mental impairment, giddiness, delirium, coma. Sensory and motor disturbances usually late. Occasional polyuria, marked slowing of speech and derangements of smelling and hearing are recorded. There may be neuralgia of the fifth and paralysis of seventh nerves.

DESCRIPTION OF PLATE XXI.

FIG. 1.—Small glandular tumour of infundibulum. Vertical antero-posterior section through the centre of the pituitary and accessory body. In the anterior lobe of the pituitary body there is a cyst containing colloid material. The posterior lobe has a characteristic lobed appearance, and is pigmented. The cystic boundary zone is well seen. Magnified 6 times. Logwood.

a. Accessory body.
ap. Anterior lobe of pituitary body.
pp. Posterior lobe of pituitary body.
s. Stalk of pituitary body.
g. Small area of glandular tissues, similar to that of anterior lobe of pituitary body.
o. Optic commissure.
c. Corpus albicans.
t. Tegmentum of crus cerebri.
e. Ependyma of ventricle.

FIG. 2.—Section of the accessory gland-like body. The cells and their nuclei are large, the cell-substance stains faintly, and not all the cells are nucleated. Numerous capillary blood-vessels. Obj. $\frac{1}{4}$ in. Oc. 4. Pillischer. Logwood.

FIG. 3.—Section of the anterior lobe of the pituitary body of same case. The structure of an average normal pituitary body is well seen. Note the difference in size and arrangement of the cells. Obj. $\frac{1}{4}$ in. Oc. 4. Pillischer. Logwood.

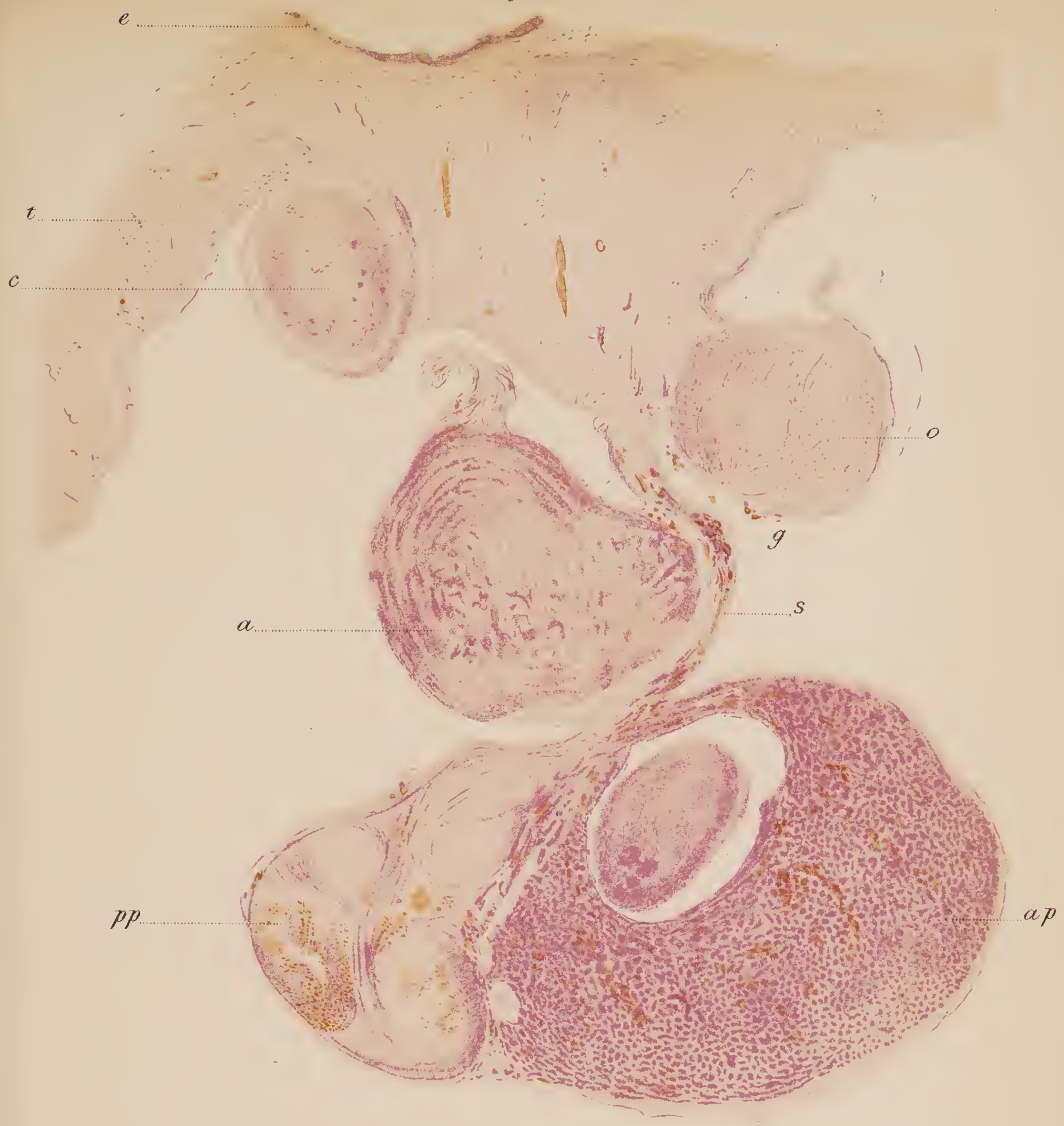


Fig. 2.

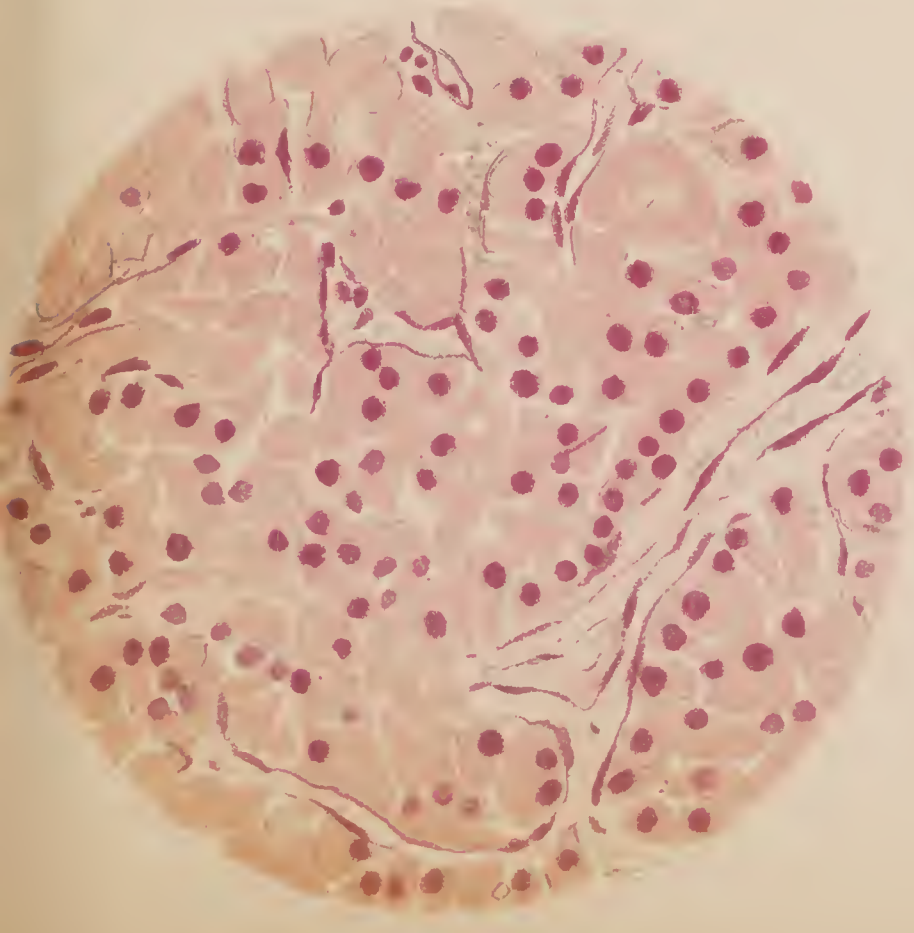
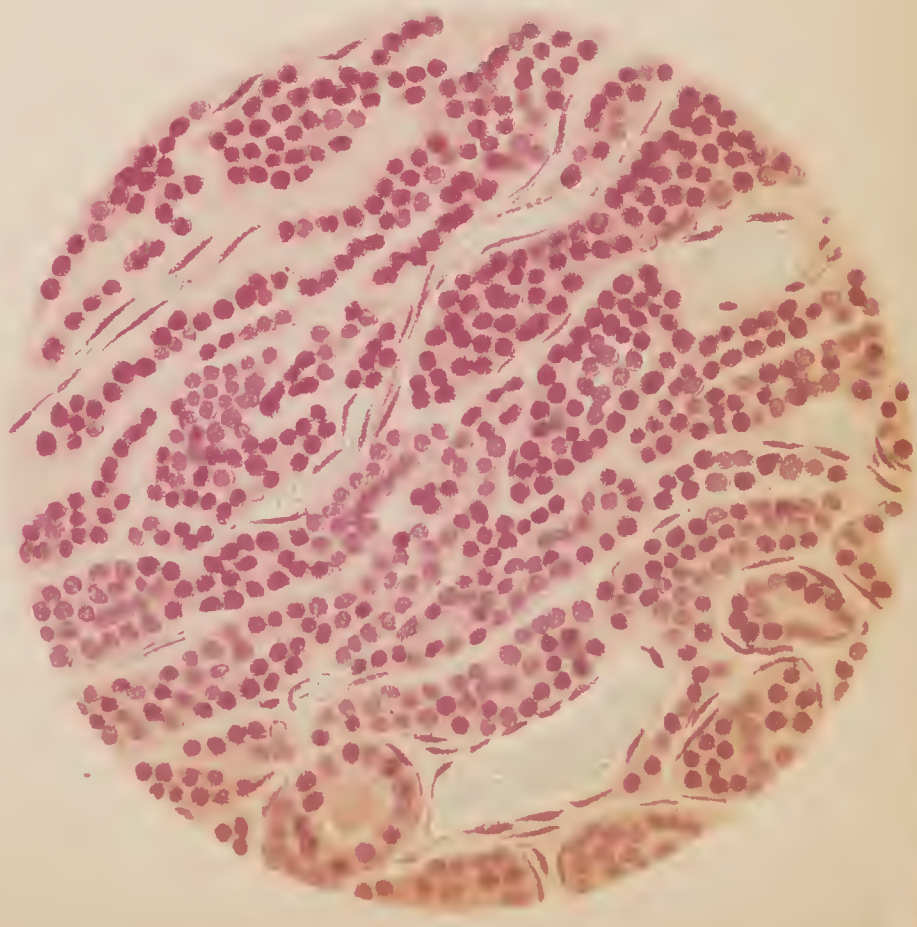


Fig. 3.



Cecil F. Beadles, del.

REMARKS UPON A CASE OF ASPERGILLAR PNEUMONOMYCOSIS.

By Rubert Boyce, M.B., *Assist.-Prof. of Pathology in Univ. Coll. Lond.*

(Plate XIII.)

From the Pathological Laboratory of University College.

The presence of the hyphomycetæ in various pathological conditions in animals and man has excited a scattered attention, more especially from the time when Virchow, in 1856,[1] carefully described three cases of pneumonomycosis. Previously, the discovery of hyphal fungi in the respiratory passages of the lower animals had been signalled by several observers, and subsequently our knowledge of the effects of the higher fungi upon the lower animals was greatly extended by the researches, of, amongst others, Grohe,[2] Block,[3] Grawitz,[4] and Lichtheim.[5] It is not my intention, however, to pass in review our knowledge of the hyphomycetæ, as this has been recently and succinctly done by Dubreuilh.[6] I wish merely to record the morphological peculiarities of one of the higher fungi, and to point out certain resemblances between it and the fungi of Actinomycosis and Madura foot, hoping that the addition of a fact, however small, may be of service in the elucidation of the life history of one of the most interesting groups of fungi.

Dubreuilh divides the mycoses into (1) those affecting birds, (2) those exciting pulmonary and other visceral lesions in mammals, (3) otomycosis, and (4) experimental mycotic affections. To these he might have added, because of the prominence so frequently given to them by Leber,[7] the keratomycoses. He states that, whilst many of the fungi are pathogenic, those which have been found associated with pul-

[1] Virchow, *Virchow's Archiv*, 1856.

[2] Grohe, *Berliner klin. Wochensch.*, 1870.

[3] Block, "Zur Kennt. der Pilzbildung in der Geweben des thiersche Organismus," Inaug. Dis , Greifswald, 1870.

[4] Grawitz, "Ueber Schimmelvegetationen in thier. Organ.," *Virchow's Archiv*, Band lxxxi.

[5] Liehtheim, *Berliner klin. Wochensch.*, 1882, and *Zeitschr. f. klin. Med.*, Band vii.

[6] Dubreuilh, *Archiv. de Méd. exp.*, 1891.

[7] Leber, "Die Ensteh. der Entzünd. u. d. Wirkung der Entzündungerreg. Schädlichkeiten." Leipzig, 1891, and elsewhere.

monary lesions in man are, for the most part, non-pathogenic. To this point I will return after the description of my case.

The notes of the case are brief and unattractive. The cause of death was cardiac disease. No prominent lung trouble is recorded, and the only reason why the apex of one lung was put by in alcohol for subsequent examination was, because it presented a few small irregular bronchitic cavities, in which were scattered white bodies, about the size of pin heads; these were mistaken for calcified foci. The lung subsequently passed through my hands, and sections readily revealed the mycotic nature of the affection.

The lung tissue is well preserved by the spirit. There exist a few small intercommunicating passages, which can be traced to dilated bronchioles. The former are lined, and in some cases plugged with a brownish-black material; where this is absent, the white points above alluded to project from the walls: in a zone of red pneumonic tissue surrounding the cavities, similar white or whitish-yellow specks are visible (Fig. 1). Teased preparations of the dark brown material show numerous conidiaphores of the type represented in Fig. 2 (Reichert $\frac{1}{12}$ oil and Oc. 18). The spores have, with one exception, been detached from the basidia, from which they appear to be formed by segmentation. Each basidium gives rise to only one row of spores. The non-fertile shoots are much more delicate than the conidiaphores, and are septate and branched. The fertile hyphæ, on the other hand, are thicker, septate, and brown. Crushed preparations of the harder white bodies projecting from the walls of the cavities, show that they are composed of hyphæ somewhat thicker than those last described; there is no calcification.

Microscopic examination of sections of the lung shows that the walls of the irregular cavities consist of lung tissue interwoven with hyphæ, which, on the inner aspect give rise to pigmented conidiaphores, and on the outer send out hyphæ, which ramify for a considerable distance in the walls of the alveoli. In places the felt work was so close that it gave rise to the pseudoparenchyma common to the higher fungi. Fürbringer[1] also describes an outer hyphal sterile zone and an inner dark pigmented one, consisting of the conidiaphores, and as in his case so in mine, the two zones could readily be detached from one another. This observer also remarks in his description of the general appearance of the fungus: "Während diese letztere (fructification zone) constant beim Zereupfen schon makroskopisch ihre Zusammensetzung aus Fäden manifestirte, stellte das Mycel eine ziemlich consistente, brüchige, homogene, bei vorsichtiger Handhabung direct schneidbare Substanz dar, die keine Spur von filziger Beschaffenheit erkennen liess." He further mentions how Küchenmeister regarded the conidiaphores as springing directly from a solid basis. But from his description of the microscopic appearances it is difficult to make out

[1] Fürbringer, "Beobachtungen über Lungenmycose beim Menschen," *Virchow's Archiv*, Band lxvi., 1876.

whether there was a complete loss of structure or not in the outer zone; he describes and figures it as simply very finely radially striated. I mention this because the mycelium of both actinomyces and mycetoma may become to all appearance quite structureless.

With regard to the structure of the tubercle-like points in the hepatized tissue, the larger nodules have a very characteristic appearance on section (Fig. 3), being made up of alternating zones of denser and looser hyphal issue; their general outline is reniform, fibres entering loosely at the hilus, then branching and weaving themselves into the dense fan-like structure figured. A comparison of this figure with those given by Boström[1] of actinomyces, shows a striking similarity in the general outlines; a reniform shape is also assumed by the mycetoma. The smaller nodules, on the other hand, have a different appearance. Thus Fig. 4 represents one which starts in the wall of an alveolus, presumably from a spore, as from one thick central stock numerous irregular processes branch out dichotomously and form a mulberry-like mass. This appearance has also been contrasted by Paltauf,[2] Lichtheim, and others, with that presented by actinomyces. The branching hyphæ, composing these smaller nodules are very irregular, and are wider and thicker walled than those found in the larger mycelial feltworks; moreover, there are no septa. Here and there in the alveoli still smaller rosettes may be encountered. Careful examination of every kind of hypha showed that in a few instances the walls were unduly thickened, and that here and there the hyphæ were embedded in a structureless matrix. I further carefully searched for the very suggestive involution forms of conidiaphores described by Fürbringer, but without success. According to this observer, the basidia may become fewer or may be absent, and the heads may become so small that the spores appear to arise from the slightly enlarged extremity of a hypha.

The tissue reaction is marked. The red pneumonic area, which spreads for some considerable distance away from the fungus (see Fig. 1), consists of alveoli filled with corpuscular and fibrinous deposits. Still nearer the centres of irritation, the lung tissue and exudates give place to necrotic débris, in which the chromatin granules of broken down leucocytes are readily recognised by their deep staining reaction. There are also very numerous liberated soot particles. At the same time, macrophages, a large proportion of which contain soot granules, become more and more abundant as the aspergillar foci are reached; they are especially numerous between the hyphæ, and a large number completely surround the latter (Figs. 4, 5, and 6). The macrophages vary very greatly in size, from little larger than the leucocyte to huge protoplasmic masses which invest a complete bunch of hyphæ (see Fig. 5); stains have very little effect upon them, the most powerful nuclear dyes rendering the nuclei only just visible; the cell substance has a very characteristic

[1] Boström, "Untersuch. u. d. Aktinomycose des Menschen," *Ziegler's Beitr.*, 1890.
[2] Paltauf, "Mycosis mucorina," *Virchow's Archiv*, Band cii.

yellow tinge, and typical amœboid outline; the pseudopodia may be long or blunt, and often have a ground-glass appearance, which contrasts with the clearer and more granular condition of the rest of the cell. Their appearance and numbers were such as at one time to lead me to entertain the idea that they were parasitic amœbœ. The hyphæ which they enclose are often attenuated, but no marked difference in staining reaction is observable.

Touching their origin I can say very little; I could not, by the aid of the various stains which I employed (see below), convince myself of their leucocytic origin, and in addition, as I have previously mentioned, a very large proportion of the latter had broken down. Indeed, I rather incline to the view that they and the familiar soot cells are distinct cell elements.

In all the sections there is a small thrombosed vessel, and examination shows that the wall of the vessel is infiltrated with hyphæ, and that many penetrate into the thrombus; it is probable that they were the cause of the clotting. A similar thrombosis has been observed by others.

One finds, on reviewing the literature, that cases of pneumonomycosis are numerous. The fungus is usually regarded as a secondary phenomenon, complicating an ulcerated or gangrenous condition of the lung, and undoubtedly the aspergilli, in man at least, are not severely pathogenic. I know of no case occurring of general infection in man. Paltauf,[1] it is true, records a case of the latter, but it was due to one of the mucorini. On the other hand Rœckl[2] describes, in the cow, a miliary dissemination of minute light yellow foci in the lung, producing pneumonia and pleurisy; the fungus had all the appearance of aspergillus fumigatus. Chantemesse[3] describes a generalised pseudo-tuberculosis in pigeons. The foci were made up of the fungus—apparently aspergillus fumigatus—giant and small round cells; caseation and pneumonia were present. Lastly, Fürbringer's case (*loc. cit.*) is very much like mine; in his case the aspergillus fumigatus was present, and this is the fungus which I have every reason to believe was present in my case. In both cases there were irregular cavities filled with dark brown material, as well as smaller white foci.

Finally, to sum up those features in the growth of the aspergillus, to which the actinomyces[4] and the mycetoma appear to bear relation—

The aspergillus may form minute, hard white, spherical, projecting masses on the walls of the cavities;

It may have a fan-like arrangement, and consist of alternating layers (see Fig. 3); or it may be completely spherical, and the hyphæ radiate (see Fig. 4);

[1] Paltauf, "Mycosis mucorina," *Virchow's Archiv*, Band cii.

[2] Rœckl, "Pneumonomycosis," *Zeitschr. f. Theirmed.*, 1884.

[3] Chantemesse, *Int. Med. Cong.*, Berlin, 1890.

[4] Domec, *Archiv. de Méd. exp.*, 1892, agreeing with others, places actinomyces amongst the mucedineæ, basing his opinion upon the terminal segmentation of the spores, and the general appearance of the fungus on culture media.

The size of the hyphæ varies; a pseudoparenchyma may be found; and very exceptionally some of the hyphæ may become embedded in a structureless material;

The fructifications may, according to Fürbringer, undergo marked involution.

With reference to the last point, Fürbringer incidentally refers to the interesting question of how far the form of the fungus is influenced by the substratum; in his own particular case diabetes was succeeded by oxaluria. He mentions the extreme view of pleomorphism adopted by Hallier, who viewed aspergillus, penicillium, oidium, and leptothrix as "form phases" of a common germ, modified by the medium in which they grow.

The stains employed included logwood, which, as is well known, gives extremely good results with the higher fungi. I found it the clearest stain. Of the aniline dyes, the fungus took up and retained the blues most readily, and the most complete differential results could be obtained with Sahli's blue and eosin. Löffler's and Kühne's blues were by no means so good. Amongst the other stains used were saffranin, fuchsin, iodine-green, Biondi's fluid, borax carmine, iodine and sulphuric acid, and Schultze's solution.

DESCRIPTION OF PLATE.

Plate XIII.

Fig. 1.—Piece of lung tissue, × 2.

a. Thrombosed artery.

b. Bronchial cavity, containing white nodules of Aspergillus, and lined by the black spore bearing form.

c. The minute tubercles of Aspergillus, surrounded by red hepatized tissue.

Fig. 2.—Conidiaphore. Zeiss Obj. $\frac{1}{12}$th in. Comp. Oc. 18.

Fig. 3.—Shows the zone and fan-like growth of a large Aspergillus nodule. Logwood. Zeiss Obj. 1 in.

Fig. 4.—Small nodule of Aspergillus arising on the wall of an alveolus, and surrounded by macrophages and tissue *débris*. Logwood. Zeiss Obj. $\frac{1}{4}$th in.

Fig. 5.—A very large macrophage, surrounding a bunch of hyphæ. Logwood. Zeiss Obj. $\frac{1}{12}$th in. Comp. Oc. 18.

Fig. 6.—Macrophages applied to, or surrounding hypha; in one macrophage the hyphal wall is quite altered. Logwood. Zeiss Obj. $\frac{1}{12}$th in. Comp. Oc. 18.

Fig. 7.—Macrophages showing the pseudopodia, and a hypha (blue) attached to one. Sahli's blue and eosin. Zeiss Obj. $\frac{1}{12}$th in. Comp. Oc. 18.

Fig 1

Fig 2.

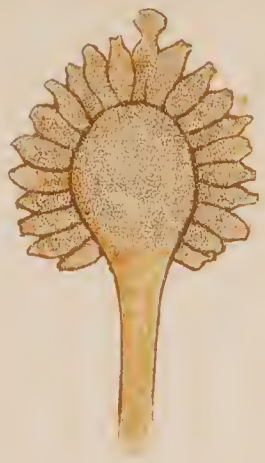


Fig. 3.

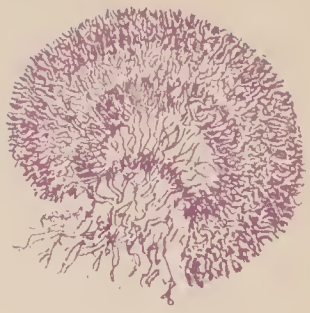


Fig 4

Fig 5

Fig 6

Fig 7

[*From the* PROCEEDINGS OF THE ROYAL SOCIETY, VOL. 53.]

"Upon the Action of Gravity on *Bacterium Zopfii*."

By RUBERT BOYCE, M.B., Assistant Professor of Pathology, University College, London, and A. ERNEST EVANS, M.B., C.M., Glasgow. Communicated by Professor HORSLEY, F.R.S. Received February 7, 1893.

(From the Pathological Laboratory of University College, London.)

(Abstract.)

Bacterium Zopfii was accidentally discovered by Kurth, in Zopf's laboratory, in the alimentary canal of the fowl. He showed it to be pleomorphic, and observed its radiate mode of growth, and, in addition, its great tendency to form spirals. It was rediscovered by Crookshank in Johne's laboratory in Dresden; this observer obtained it from the air, and likewise noted the characteristic pinnate mode of growth. He named it *Bacterium figurans*, on account of its figured appearance upon the solid nutrient media. We obtained it from a case of otitis media in the cat, in London. These observations show that the organism is probably widespread.

Mode of Growth of the Bacterium.—On gelatine it forms, under certain circumstances, a feather-like or pinnate growth upon the surface and in the gelatine, the branches of which are directed upwards at about an angle of 45°. Under no circumstances (according to our observations) does it form a pinnate growth upon agar or potato.

Action of Gravity.—The symmetrical pinnate growth could not be obtained in gelatine tubes which were kept horizontal or nearly so, whilst similar tubes kept vertical or nearly so exhibited the characteristic growth. A certain scale of symmetry could be obtained by placing the tubes at various angles between the vertical and horizontal. If a tube in which a pinnate growth had been obtained was completely reversed, a new pinnate growth might be seen to cross the first, but it was not so marked as the latter. These observations showed that *Bacterium Zopfii* was markedly susceptible to position, and that the pinnate growth could only be obtained in or about the vertical. They pointed strongly to the influence of the action of gravity.

Behaviour on the Clinostat.—If the force of gravity acting upon the culture tube in the one position were prevented by slowly revolving the growth in the vertical at rates from one revolution in one minute to one in one hour, then the pinnate growth could not be obtained. We assumed, therefore, that *Bacterium Zopfii* was subject to the action of gravity, and that it was *negatively geotropic*. But if it were

negatively geotropic, then it ought also to assume a *centripetal* direction if rapidly revolved.

Action of Centrifugal Force.—We repeated Knight's experiment, communicated to the Royal Society in 1806, and revolved the culture tubes in the horizontal at the rate of three to five revolutions per second, and we obtained most perfect pinnate growths, similar to those obtained by growing in the vertical.

The Cause of the Pinnate Growth.—The growth is very rarely orthogeotropic; there is a force hindering this, which we believe to be the *resistance of the gelatine.* Although the pinnate growth appears superficial, this is not so; the filaments tend to dip slightly or deeply into the substance of the gelatine. It is observed that where they penetrate deeply into the gelatine they are almost horizontal at the bottom of the gelatine, whilst nearly vertical at the top of the gelatine column. These differences are still more accentuated when the tubes are centrifugalised.

Circumstances which Favour or Retard the Symmetrical Growth.—It is essential that the gelatine be not too stiff; if it is hard, an irregular superficial or an imperfect pinnate growth obtains. We employ a freshly prepared 8 to 10 per cent. nutrient gelatine. A slight variation in the *reaction* on the acid or alkaline side of neutrality makes no appreciable difference. *Temperature* has a very important effect; symmetrical growths are with difficulty obtained at low temperatures; the most suitable is that between 20° C. and 21° C. *Carbonic acid* hinders the symmetrical growth; oxygen favours it. Thus, if a streak culture on gelatine is placed in an atmosphere of CO_2, at the end of three days there is only a thick streak along the line of inoculation; if the tube is then transferred to oxygen, a symmetrical growth develops in the course of twelve to twenty-four hours. We have not yet observed any difference in the growth in the colours of the *spectrum.*

Not only has the hardness of the gelatine a marked effect upon the pinnate growth, but in addition the *thickness* of the gelatine substratum is important. Thus, we never obtained pinnate growths in our method of plate cultures on microscope slides. Even in Petri boxes, with a thickness of gelatine varying from $\frac{1}{4}$ inch to 1 inch, the *growth upon the surface* often tended to be irregular, but in these cases the filaments which grew deeply into the gelatine assumed the pinnate form, with the exception, as before mentioned, that the lowermost branches were more horizontal than those at the top. Thus, to obtain a pinnate growth upon the surface, the test-tube is the best culture glass.

Microscopic Characters of the Growth.—The organism is pleomorphic; filamentous, bacillary, bacteroid, spiral, and coccal form phases being met with. There is also a motile stage, in which bacillary, bacteroid,

and coccal forms predominate; there appears to be an absence of the motile spiral form. In the motile phase there is a very slight liquefaction of the gelatine, but for the rest there is no liquefaction of the gelatine. In addition to the differences of form of the separate elements, there appear certain phases in the grouping of the bacteria. Thus, following Billet, we divide our growths into *filamentous*, *disassociated*, *skein*, and *zoögleaform phases*. The *filamentous form* is especially met with in gelatine, and in the pinnate growths the filaments are at first very long and hyphal-like, and are rapidly growing, but segmentation follows early. If branching occurs it appears to take place as in *Cladothrix*, by displacement of segments. In the *disassociated phase* the segments break away from one another, and may become motile. The *skein phase* is met with on hard gelatine and on agar; it is a very superficial growth, and the filaments form dense plaits; it is not met with in geotropic growths. The *zoögleaform phase* is very characteristic, and usually rapidly follows upon the filamentous. In the filaments and segments multiplication occurs either at scattered points in the chain or throughout its length, and the segments remain united by a common cementing substance; the forms assumed by these aggregates are very beautiful, and are to be met with in the geotropic growths.

The Spirillation.—The undivided or segmented filaments and the zoögleaform masses have a marked tendency to twist, especially in the pinnate gelatine cultures. The majority of the twists are in the opposite direction of the hands of the clock. Kurth noted the spirillation, and attributed it to the resistance of the gelatine; but as in the higher plants, perhaps here, the action of gravity is also a factor. This consideration also opens up the meaning of the spiral form in the bacteria.

Methods of Fixing and Staining employed.—Our preparations, from which the micro-photos were taken were obtained from plate cultures made in the following manner:—A micro-slide in a large sterilised test tube is coated with a thin surface of sterilised gelatine by means of a balloon pipette. After solidification the surface is inoculated with a streak. The growth may be examined either unstained or after fixing and staining. To fix, the slide is withdrawn from the test-tube and placed in dilute alcohol, and then dried; any stain can then be employed, and the preparation mounted in Canada balsam.

HARRISON AND SONS, PRINTERS IN ORDINARY TO HER MAJESTY, ST. MARTIN'S LANE.

[*From the* Proceedings of the Royal Society, Vol. 53.]

"Upon the Existence of more than one Fungus in Madura Disease (Mycetoma)."

By Rubert Boyce, M.B., M.R.C.S., Assistant Professor of Pathology, University College, London, and Nusserwangi Fakirgi Surveyor, M.D., M.R.C.P. Communicated by Professor Victor Horsley, F.R.S. Received February 21, 1893.

(From the Pathological Laboratory, University College, London.)

(Abstract.)

Nature of Mycetoma.—A very chronic, locally spreading inflammation of the foot, much less commonly of the hand; characterised by the destruction of the tissues, great overgrowth of granulation tissue, and by the presence of very numerous *brown-white*, fish-roe-like particles, or more rarely of *black* particles.

Views held concerning Mycetoma.—In 1874, Carter held that the "fungus foot" was a veritable parasitic disease, due to the growth and extension, within the tissues, of an "indigenous mould." He came to the conclusion that it was one species, the *Chionyphe Carteri.* Lewis and Cunningham (1888) concluded that mycetoma was "essentially a degeneration of the fatty tissues, independent of the local presence or influence of any parasites whatever." Bassini (1888) met with a case in Italy, the only one, as yet, observed in Europe, and concluded that the parasite was allied to the higher Fungi, either the Aspergilli or Mucorini. Most recently, Dr. Kanthack brought forward evidence to show the identity or close affinity of the parasite with that of actinomycosis.

Our Views.—That the black particles represent a curious metamorphosis of a large, branching, septate fungus; whilst the white particles consist largely of caseous material and of the remains of a lowly organised fungus, presenting in very many instances some of the characteristics of the fungus of actinomycosis. That both fungi are pathogenic. The following observations in support of these views are based upon an

examination of seven specimens of the black variety and of eighteen of the white, obtained from Bombay and from the various museums throughout the United Kingdom.

Black Variety.—Sections of the particles, free or *in situ* in the tissues, show that they are composed of tufts of a deep brown colour, and apart from a faint radiation or the presence of a slight venation or of holes, they give very little indication of a vegetable structure. By boiling the particles for from a few minutes to one hour in concentrated caustic potash, the brown colouring matter is very slightly removed, but this is completely discharged upon transferring them to distilled water; the fungus can then be readily studied. The animal tissues are however, destroyed by this process. If, however, the tissue containing the particles is embedded in collodion, washed for about one minute in "*eau de Javel*," and then stained, the colouring matter is removed from the fungus, and its relationship to the tissues around can be readily seen. The *fungus* appears the same in all the specimens of the black; the hyphæ radiate and branch, the segments vary very greatly in size; they may be spherical and reach a very great size, or long and slender; a pseudo-parenchyma may be formed in the centre of a tuft, or a palisade at the periphery. We have seen no organs of fructification. *Tissue reaction.*—The tufts are embedded in granulation tissue or necrosed material, and the presence of very large giant cells and other phagocytes is characteristic. The hyphæ may penetrate the vessels and run in their interior. The *metamorphosis* of the fungus appears to take place very early and affects equally the various hyphæ throughout the tissues. The nature and meaning of the change is very obscure. The dried particles burn with a luminous flame. Incinerated, there is a slight smell of burnt feathers, and in the ash, which is very little, there is a brown coloration, owing to the presence of iron; the presence of the latter may be confirmed in the unclarified and clarified specimens by the Prussian blue test. The iron is, however, limited to the periphery of the tufts, and appears wholly derived from the animal tissues. The particles give a red reaction with dilute nitric and hydrochloric acids: little impression is produced upon them by boiling in the various fat solvents; they give no special reactions with ferric chloride or cupric acetate (resin test).

White Variety.—Sections of the particles are characteristic. In the centre are usually numerous small reniform deeply-staining masses, surrounded by a deep radiate zone. In the central bodies a very fine reticulum may occasionally be made out; more usually, stronger evidence of the fungus is obtained by the presence of dwarfed club-like hyphæ, which form an irregular fringe to the reniform bodies. It is exceedingly difficult to ascertain what gives rise to the deep radiate zone; the leucocytes in it are compressed, yet the compressing

hyphæ remain for the most part unstained. The fungus undergoes very early degeneration. *Tissue reaction.*—The particles are surrounded by leucocytes and are either embedded in granulation tissue or lie free in the abscess cavities or sinuses.

In both varieties the spread of the particles and inflammation goes hand in hand, and a recurrence of the particles and of the inflammation has been observed by one of us in the scar left after amputation for the black variety of fungus foot.

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MADURA DISEASE.

At a meeting of the Pathological Society of London, held on Tuesday, April 18th, Sir George M. Humphry, F.R.S., President, in the chair, Dr. Boyce and Dr. Surveyor (who was introduced by Dr. Boyce) contributed a paper on Madura Disease (Mycetoma Carteri).

They stated that mycetoma was a very chronic, locally spreading inflammation of the foot and much less commonly of the hand. As the specimens exhibited showed, it was characterised by much tissue destruction as well as by hyperplasia, but especially by numerous light-brown fish-roe-like particles, never yellow and less commonly black. Its scientific history dated from Dr. Vandyke Carter's researches. The disease usually occurred in people who went barefooted and worked in fields. In most cases it had been traced to some injury. It usually stopped at the ankle for a short time, then spread up to the knee and eventually might even reach the thigh. In one case there had been a recurrence of the black variety in the wound, and one of the authors expected shortly to receive a specimen of the white variety in which the disease recurred in the scar after a period of about two years. These cases, however, were rare, and amputation generally afforded complete relief. But generalisation had not been recorded. There was considerably more hyperplasia in the white variety. On the other hand, in the black variety the external appearance of the part might give but little indication of the widespread internal destruction and the enormous accumulation of the black masses. The latter were often encapsuled by dense tissue, whilst the white particles were equally often surrounded by young granulation tissue. The appearance of the black variety suggested, in many cases, the enclosure in the tissues of foreign bodies which

had long ceased to produce irritation. With the elucidation of this variety they had been chiefly concerned and they should more especially confine themselves to the demonstration of its structure. The particles varied greatly in size—from that of a grain of gunpowder to a marble. Sections of the particles, free or *in situ* in the tissues, showed that they were composed of tufts of a deep brown colour, and apart from a faint radiation or the presence of a slight venation, they gave very little indication of a vegetable structure. In these particles some observers (Carter, Bristowe and Bassini) obtained evidence of a septate fungus. Drs. Boyce and Surveyor found that, if the particles were boiled for from a few minutes to one hour in concentrated caustic potash, brown colouring matter was very slightly removed, but that this was completely destroyed upon transferring them to distilled water. The fungus could in this way be readily studied, but the animal tissues were destroyed. If, however, the tissue containing the particles were embedded in celloidin, washed for about one minute in eau de Javelle and then stained the colouring matter was removed from the fungus and the latter's relationship to the tissues around could be readily seen. Specimens under the microscope and the projections illustrated this. The fungus appeared to be the same in the specimens of the black variety. The hyphæ, which were usually very large, radiate and branching, resembled, as Bassini had already suggested, the higher fungi. The segments might be spherical and a pseudo-parenchyma might be formed or the hyphæ might form a palisade at the periphery. They had never seen organs of fructification. The tufts might be surrounded by necrosed granulation tissue ; large giant cells and phagocytes were, however, characteristic. The sections showed that the hyphæ might penetrate vessels and run in their interior. The metamorphosis of the fungus which led to the formation of the apparently structureless black masses probably set in early and rendered the fungus inert. In the large particles there was a slight amount of iron present, as shown by the Prussian blue and other tests ; it appeared to be wholly derived from the surrounding tissues. The particles turned red with dilute nitric and hydrochloric acids ; little impression was made upon them by boiling in various fat solvents. There was a great contrast between the white and black varieties. In a very

large number of cases the evidence of the presence of a fungus in the so-called fish-roe-like bodies was very little, the particles being little more than caseous and calcareous lumps. Sections of the particles were for the most part characteristic; in the centre there were usually numerous, small, reniform, deeply staining masses, surrounded by a deep radiate zone. In the central bodies a very fine reticulum might occasionally be made out; most usually stronger evidence of the fungus was obtained by the presence of dwarfed, club-like hyphæ, which formed an irregular fringe to the reniform bodies. In appearance, therefore, the white particles resembled actinomyces. They were surrounded by leucocytes and were either embedded in granulation tissue or lay free in abscess cavities or sinuses. (The paper was illustrated by some excellent micro-photographs.)

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THE MORPHOLOGY OF TUMOURS.

Read in the Section of Pathology at the Annual Meeting of the British Medical Association, held in Nottingham, July 1892.

BY RUBERT BOYCE, M.B.,
Assistant Professor of Pathology, University College, London.

DR. BOYCE demonstrated a photographic record of some of the leading types of the epitheliomata in order to show the grounds upon which he was seeking to establish a division of tumours upon a morphological basis.

In the present instance he had selected the skin tumours, having elsewhere expressed his views upon those of the mamma and glands generally. He thanked Dr. Crocker and Messrs. Johnson, Stephen Paget, Walter Spencer, White, and Beadles for abundance of material. Up to date he had examined 250 cases. Recently a great zoologist had expressed the opinion that it might be possible that the neoplasmata belonged to the category of miasmatic diseases. This statement, coming from Metschnikoff, had naturally directed attention to the minute anatomy of the cell. He would, however, chiefly confine his remarks to the various forms assumed by cell aggregates and to the difficulties which presented themselves in accepting the theory of a contagium vivum.

Continuing, he said: It is seventeen years since Thiersch published his work upon skin cancer, and he has this year the satisfaction of finding in the *Festschrift* recently presented to him that his theories have held their own during this period. It is precisely seventeen years also since Virchow published in his *Archiv* a description of molluscum contagiosum, and it is only a few months since he had the satisfaction to learn in the *Festschrift* presented to him by his former and present assistants that his description of molluscum contagiosum and of the peculiar bodies found in it remained good. During this period of seventeen years the interest taken in cancer has not ceased. At first the morphology occupied the attention of pathologists; then came a more close examination into the etiology of cancer. Cohnheim looked to a congenital fault, others to irritation, as determining factors in the etiology of cancer. The relationship of "irritation" to neoplasis has increased in prominence. As is well known, psoriasis lingualis, laryngis, nasalis, and præputialis, and the seborrhœa senilis of Richard Volkmann have engaged, and still engage, very considerable attention. Schuchard in 1885, Rudolph Volkmann in 1889, and others have brought together a very considerable number of surface tumours which were preceded by long-standing sources of irritation, such as, for example, obtained in soot sifting, tar and paraffin working, chronic sinuses, and lupoid and syphilitic ulceration. Amongst other researchers engaged upon these or similar

lines may be mentioned Boegehold, Hauser, Heitter, Kuttner, Zenker, Butlin, Posner, Kanthack, and Hutchinson.

In the meantime some were stimulated to seek a specific bacillus for cancer. The number of these researches was not great. One of the first was Wédopil, in 1881, but Scheuerlen obtained most notoriety; he appears to have based his results upon two experiments. It may be mentioned that the priority of Scheuerlen's claim was disputed by Schill and Frière. The simple culture experiments of Ballance and Shattock, and the beautiful monograph of Hauser, appear to have stopped the further search for a specific bacillus, although indeed an account of a specific contagium under another name was published in this country. It is well understood of course that pathologists do not deny to bacilli, or to any other parasite, a very important position in the processes known as irritative; take for example carcinoma aris ing in lupus and in syphilis, and in distomatosis.

In 1873 Bollinger described a truly enigmatical contagious epithelioma in the hen, and was able to infect healthy hens. He likened the tumours in structure to Virchow's epithelioma contagiosum. Israel, however, in 1892, says that it resembles an ordinary epithelial downgrowth. Bollinger described no contagium vivum. Weisser, in 1888, and Moreau, in 1889, described parasitic bodies in molluscum contagiosum. Then commenced the numerous researches by a group of French observers—Darier, Wickham, Malassez, Albarran, Soudakewitch, etc.—upon coccidia-like bodies in tumours. In the meantime, in Germany and elsewhere, the coccidia question had occupied considerable attention from amongst others—Pfeiffer, Sjöbring, Thoma, Podysoski, Delépine, and very recently Ruffer, and the numerous others to whom references will be found in the writings of Stroebe and Steinhaus. Very many of these observers have taken very strong views, just as Scheuerlen has done. On the other hand, histologists like Thoma, hold themselves very reserved. Recently too, Stroebe, Steinhaus, O. Israel, Karg, Eberth, Ribbert, Hauser, and Delépine, have paid very considerable attention to the nature of these bodies, and I think I may say that they agree with what Virchow said seventeen years ago, and which he has again repeated, namely, that as no previous and no subsequent stages of these bodies can be traced, therefore there is not sufficient evidence as yet in support of their parasitic nature. They term them, in consequence, cell enclosures which may be of endogenous or leucocytic origin. Moreover the majority of these last mentioned observers very strongly go against the idea of a specific contagium. For in truth the difficulties in the way of a theory of a contagium vivum, based upon our present knowledge, are immense. Carcinoma is but a genus of the neoplasmata, the other members of which are the fibrous, fatty, cartilaginous, muscular, and other tumours; they merge into the teratomata, giant growths, elephantiasis, etc., of congenital origin. I will attempt to show in the skin tumours that on morphological grounds we may be able in very many cases to decide whether certain neoplasms are of congenital or of acquired origin—whether, in other words, the cancer springs from a "rest," the "fault" or "irregularity" of Cohnheim—and which may be formed at the period when the tissues are undergoing their differentiation; or whether, on the other hand, it springs from adult tissue. In the latter case irritation undoubtedly appears to play a most important part, and

numerous causes of this irritation have been admitted or proved, such as parasitism and mechanical irritation; we however by no means imply any specificity of virus in this assumption. Rudolf Volkmann, working on other lines, came to the conclusion, from his analysis of epitheliomata of the extremities—one of the largest and best which has ever been made—that those epitheliomata which arose from congenital moles, nævi, etc., though few in number, had to be separated from the very large group which resulted from acquired warts, ulcers, and chronically irritated parts generally. He pointed out that the tumours of irritative origin were practically benign; on the other hand, those which arose in congenital marks were exceptionally infective. The preceding observations must I think be taken into account by researchers engaged upon a contagium vivum, as it is obvious that they are a source of difficulty. Whether my own observations will, from the clinical aspect, agree with those of Volkmann I am as yet unprepared to say. Here I may mention that it would be worth the while of the statistician, when he states that cancer is on the increase, to bear in mind the possibility of a division of neoplasms into the congenital and acquired. He would understand that we could have little control over the former, but he would know from history that circumcision appears to have abolished preputial cancer, and improvements in methods of manufacture and of factory hygiene appear to have diminished the form of cancer more particularly associated with the trades.

Cancer, it has been asserted, has every appearance of being due to a living contagium, and undoubtedly cancer may become a terribly infective disease. Further, Novinsky, in 1876, and later Wehr and Hanau, succeeded in inoculating animals, and Hahn and Bergmann the human being. Cancer is, however, an infectious disease which differs from all other known infectious diseases. The secondary foci are grafts of the original focus, which do not confer their malignancy or their infectivity on the tissues around; the metastatic focus of the skin cancer in the liver does not produce, as far as we know, an adenoma of the latter organ. Why, asks Karg, if cancer is infective in the ordinary sense, does not, for instance, œsophageal cancer, when it bursts into the trachea, produce an epithelioma of the trachea? If there is a specific cancer organism like the specific organisms with which we are at present acquainted, then it is obvious enough that there must be one for the squamous epithelium, one for its appendages, one for the liver, and so on. But, it may be argued, there is a symbiosis between the parasite and cancer cell. This is introducing a hypothesis more difficult of comprehension than the theories of Klebs and Schleich. As a matter of fact, the abnormalities of the cancer nucleus have received considerable attention from Hansemann, the pupil of Arnold, and from Klebs, Schleich, and others. Hyperchromatosis is sometimes extremely marked. It is therefore not, perhaps, extravagant to assume for the cancer cell a fusion of chromatins comparable to that which takes place in the egg cell. At any rate, the nucleus appears in the vast number of cases to be abnormal.

To return to the bodies found in cancer cells. It is evident that the large proportion of observers describe the same bodies, but unfortunately they have almost all neglected Koch's most important advice to photograph them. Thus Sjöbring describes a parasite in cancer the life-history of

which it has been pointed out tallies in a most remarkable manner with that of the plasmodium malariæ. The psorosperm bodies of the French observers are for the most part very large. Boeck has recently figured Darier's parasite in a case of Darier's disease, which has very considerable dimensions, but Boeck does not take it for a parasite. Karg takes the precaution to photograph a section of the epithelium in a case of Paget's disease; and in that photograph Karg says the bodies described by Wickham can be seen. In my own morphological studies I have paid considerable attention to the cancer cell enclosures. I have in common with others found them to be of variable frequency and of very different appearances, but I have found nothing as yet which would lead me to conclude that they were animal, but it may be that they will be proved to be parasitic. I cannot, however, as yet understand, for the reasons above given, how they will be proved, if parasitic, to be specific—that is, basing my opinion on what we know of infective processes. With regard to the presence of animal parasites in cells, I may here point out that I have elsewhere shown that those parasites, like the sarcosporidia, coccidia, and trichinæ, which dwell in cells, for the most part excite extremely little cell reaction; but I have also pointed out that these same parasites may, for reasons which we know not, give rise to necrosis or neoplasis.

But with all the above difficulties in the way of the theory of a specific virus for cancer, we have the opinion of Metschnikoff, and both his opinion and that of Malassez—though the latter's evidence appears to have been somewhat shaken—is entitled to the greatest respect. At the same time, I think that those who throw out the hint of a contagium vivum should express themselves more clearly upon the manner of infection.

[Dr. Boyce then showed sixty-five photographs arranged into groups, each group showing peculiarities of its own. The first group showed epitheliomata which were preceded by hyperplastic changes, or increased eleidin, horny or mucoid formation. They were stated to be associated with chronic inflammatory processes, and there was usually a considerable number of leucocytes and lymphocytes. The second group embrace the fibro-epitheliomata, in which the preponderance of a spindle-celled stroma was striking from the commencement; these growths had been called scirrhoid cancers of the skin. The third group embraced what Dr. Boyce believed to be congenital epitheliomata; they were very striking growths, both on account of their stroma and epithelium; they included the branchiogenous carcinomata. The fourth group showed the origin of a very common form of rodent ulcer in sebaceous glands; but what may be regarded as endotheliomatous and hair follicle types were also seen. The fifth group showed hair follicle epitheliomata, commencing with molluscum contagiosum. Under this category he would include a cystic and papillomatous epithelioma found in the lip and penis. Photographs were also shown of the bodies found by Virchow in molluscum contagiosum, by Karg and Wickham in Paget's disease, and one by Dr. Boyce in rodent ulcer.]

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SPOROZOA AND CANCER.

At an ordinary meeting of the Pathological Society of London, held on March 7th, the President, Sir George Humphry, in the chair, the debate on the Pathology of Cancer and Sarcoma was resumed by Mr. Rubert Boyce, who detailed the results of researches on cell inclusions in cancer which had been made by himself and Dr. Arthur Giles.

He showed micro-photographs illustrating some phases of cancer bodies which they had recently met with in a case of carcinoma of the pancreas. The sections were all equally and highly magnified; they were hardened in alcohol and stained with logwood. As Dr. Galloway hinted at the last meeting, in his clear summary of his own broad views, they were inclined, from want of stronger evidence, to believe that many of the parasitic bodies so recently described in cancer cells were not parasitic, but of the nature of endogenous cells. Whilst the processes of cell invagination and of nuclear and cell-plasma degeneration had been discussed by those holding the parasitic view, endogenous cell formation had been briefly dismissed or left out of account; yet this process was the one *par excellence* which must be sharply differentiated from parasitic enclosures, for the endogenous cell and the parasite were alike nucleated protoplasmic masses, and the unicellular parasites of certain mollusca, as well as those found occasionally in the alimentary tract and lungs of man, showed how very difficult it was to distinguish between the parasites and certain cells of the host. The confounding of the two in the past had led to curious mistakes upon both sides—notably, on the one hand, in the mistaking of the parasites of the blood-corpuscles of the frog for active phenomena of the protoplasm of the corpuscles themselves; and, on the other hand, in regarding certain

nuclear forms as parasites. Arnold, who had done for pathological mitosis what Fleming did for the normal process, described and figured endogenous cell formation in the giant cells of marrow, of tuberculous glands and of neoplasms. A glance at his figures showed how closely this phenomenon resembled the appearances of parasitism as described by recent observers. Recently a paper had appeared from Arnold's laboratory by Müller, in which the parasites described by Drs. Ruffer and Walker are regarded as typical examples of endogenous cell formation. Müller's figures agreed with the photographs they were showing and they thought that they were correct in saying that both were identical with the appearances described and figured by Drs. Ruffer and Walker, Dr. Galloway, Mr. Clarke, and others. Their preparations showed :—1. That the cell enclosures were met with in abnormal cells. They were giant forms ; there was very often more than one nucleus ; there was the very marked hyperchromatosis so characteristic of many forms (especially giant forms) of sarcoma and carcinoma cells. There were evident signs in many of the giant cells of dropsy of the plasma. This dropsical condition was represented by a loose reticulation of the cell substance, or by the formation of groups of vacuoles. These observations accorded with those of Müller. 2. That the cell enclosures were single or multiple, and that they usually commenced in or near the nucleus or that they occupied the place of the nucleus. These observations agreed with those of Arnold, in which the nucleus of the included cell was often connected by fine chromatin strands with the mother nucleus. 3. That the enclosures consisted either of little else than chromatin granules or of a nucleus and protoplasm. That the chromatin of the enclosed cells might be broken up into several pieces or may appear as if about to divide. The chromatin might be separated by an enclosing vacuole from the rest of the cell, and often stained just like the nucleolus of the mother nucleus. 4. That there was a capsule which was regarded by Dr. Ruffer as formed by the cancer cell itself. Dr. Galloway observed that it might be radially striated, and they had met with one very marked example of this. They called attention to a highly important and little known observation of Flemming's—namely, that the capsule of the fat cell was highly differentiated and might give a distinct staining reaction. With regard to the explana-

tion of the thickened and striated capsules, perhaps some information might be obtained from Stilling's observation upon the encapsuled endogenous bodies found in the prostate. 5. That the capsule expanded, either by the growth of the enclosed body or by the accumulation of fluid. Capsules might, in fact, contain perfect cell enclosures, large or small granular masses (spore-like bodies), fine granular *débris*, or only fluid. They had found all connecting stages of these conditions. 6. That when several capsules were formed in the same cell or in close proximity a mulberry mass resulted comparable to the mulberry fat cells (derived from one cell) of certain of the lower animals. The partitions might, however, rupture and fusion occur. 7. That capsules were met with enclosing more than one nucleated body. There might be two or more perfectly formed cells, or, on the other hand, very degenerate masses. These groups appeared to them a most suggestive feature from the point of view of parasitism. 8. That there was not the least trace of irritation or leucocytic reaction in the neighbourhood of the cell enclosures, and that the cancer cells in these parts did not show any greater signs of activity than elsewhere. From the above facts they did not feel justified in concluding that these bodies were parasites, and the great variety of appearances described by different observers seemed to them rather to favour the non-parasitic view. Mr. Boyce and Dr. Giles were of opinion that Mr. Clarke brought forward to the Society no evidence whatever to show that "both cancer and sarcoma were caused by the parasites in the same sense that tubercle was caused by the tubercle bacilli." Cancer gave rise to metastasis, but the secondary foci, unlike tubercle and the infective processes generally, were grafts of the original focus, which did not, in so far as we at present knew, confer their malignancy or their infectivity on the tissues around. Mr. Clarke and Dr. Galloway admitted as parasites free nucleated bodies, described as amœboid by Mr. Clarke in the intercellular spaces. Dr. Ruffer and others, on the other hand, restricted the term "parasite" to encapsuled cell enclosures. From the analogy of parasites in the lower animals the one view had at least as much in its favour as the other. Cancer bodies had been freely compared with and called "sporozoa"; they would, however, call attention to the following points, in which cancer bodies and sporozoa were in marked contrast:

1. The intra-cellular sporozoa (sarcosporidia) seemed to be of a harmless nature, not causing inconvenience to their host (Bütschli), but rather living on terms of symbiosis, which is well illustrated in the paramœcium, where it might be even hereditary; but, to quote Dr. Ruffer, "the life of the parasites in the cancer cells is a precarious one," whilst "they cause their hosts to perish." 2. Sarcosporidia were nearly always large and visible to the naked eye. 3. The cystic, or resting stage of sporozoa was the only one represented at all definitely among cancer bodies. They never saw the active amœboid stage, pseudopodia or ciliated forms, as seen in Coccidia and Klossia. 4. The numerous round lenticular or falciform spores, so characteristic of sporozoa, were never seen in cancer. 5. The bodies which had been compared to spores were clear, like fat globules, and of unequal size. Spores of sarcosporidia were invariably of uniform size and generally granular. 6. The spores of gregarinidæ always had a silicious or chitinous capsule. To conclude, they must still agree with what Virchow said eighteen years ago, and which he had recently repeated—namely, that as no previous and no subsequent stages of these bodies could be traced, therefore there was not sufficient evidence as yet in support of their parasitic nature.

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A PRELIMINARY REPORT ON ŒDEMA.

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Since the process of transudation is essentially a vital one, it will long remain a fertile source of inquiry to the physiologist; it is still more important to the pathologist. The passage of fluid from the circulating blood through the wall of the blood vessel into the cell spaces and then into the capillary lymphatics was supposed by Lower in 1669 to be due to mechanical pressure in the blood vessels produced by venous stagnation. This idea has survived to the present day. As a matter of fact, of course, the complex processes of living tissues are not to be so easily explained by the simple statement of Lower. Two hundred years after Lower (namely, in 1869) Ranvier proved that another factor must be considered, namely, the action of the nervous system. We will subsequently return to the discussion of his facts, which have received scant attention in this country.

Enumeration of Various Factors in the Production of Œdema.—Twenty years after Ranvier we have the remarkable researches of Heidenhain, in which the concurrence of the various factors is first stated comprehensively, in a thorough and accurate analysis. Being responsible in lecturing on general pathology for giving a reasonable exposition of this commonly supposed simple subject, we have always felt the necessity of setting on foot further investigation of the questions it involves. Having with

this object entered on a research of this kind, we intend on this occasion to refer only to certain points that may be readily illustrated, and to formulate, if possible, the distinct questions which are really embodied in the single word "œdema." Stated categorically, the several divisions of the subject on which information must be obtained are as follows :—

(1) The chemical and morphological constitution of the blood.

(2) The condition of the so-called vasoconstrictor spinal nerve centres.

(3) The condition of the peripheral vasomotor centres.

(4) The condition of the peripheral vasomotor nerve fibres.

(5) The possible existence of vasotrophic nerve fibres.

(6) The possible existence of vasosecretory nerve fibres.

(7) The condition of the nerve endings of the fibres named in 4, 5 and 6.

(8) The condition of the endothelium of the blood vessel wall.

(9) The condition of the other tissues of the blood vessel wall.

(10) The condition of the ground substance and cell spaces.

(11) The condition of the connective tissue corpuscles.

(12) The condition of the nerve fibres and nerve endings in relation with the connective tissues.

(13) The condition of the endothelium of the lymph vessel wall.

(14) The condition of the other tissues of the lymph vessel wall.

(15) The condition of the nerve fibres and endings in relation with the lymph vessel wall.

(16) The chemical and morphological constitution of the œdema fluid.

(17) The chemical and morphological constitution of the lymph.

(18) The pressure and rate of flow of the blood.

(19) The pressure and rate of flow of the lymph.

It will be seen that in truth the facts of normal anatomy and physiology on several of these points are wanting.

The Insufficiency of Physical Theories.—We believe, however, that it will not be useless to state what remains to be done as well as to discuss what has been accomplished. In

the first place, as regards the possibility of finding an explanation of the phenomena in simple physical considerations. It is not going too far to assert that the remarkable paper by Tigerstedt and Santesson[1] disposes, once and for all, both of the conclusions that have been derived from physical considerations, and of the claim that the process of transudation in the living body is capable of interpretation by mere variations of pressure on the sides of a permeable membrane.

What is Venous Stagnation?—It is essential that we should formulate our views on this matter, since no greater error exists than as regards this oft-spoken-of factor. Since venous anastomosis is so free, it is self-evident that the term "venous stagnation" must always be relative and not absolute. Not only is this to be considered so far as the mere distension of the vessel is concerned, but also as regards the part or tissue in which the stagnation is occurring. Of these two points we will now give examples drawn from our experiments.

The Proportionate Degree of Distension.—In a dog in which Ranvier's experiment of retroperitoneal ligature of the vena cava and concurrent section of the sciatic nerve was performed, no œdema whatever occurred, not even in the thigh. Moderate enteritis was present, but on killing the animal the remarkable and—according to Professor Ellenberger, who kindly wrote to one of us on the point—rare anomaly of a double vena cava, was found. Venous stagnation here, therefore, must have been very low in consequence of the unforseen anastomosis. There was a remarkable turgidity of the fat about the bladder, which is a very constant lesion after the ligature of the cava. The degree to which this is developed is conceivably proportional again to the same thing—namely, freedom of anastomosis—but also to the looseness or distensibility of the tissue involved. Further evidence in favour of the former of these views is shown by the fact that in the female—in whom, of course, the anastomoses are very free, and the ovarian and uterine veins large—this turgidity of the perivesical fat is rarely marked, whereas it is at its acme in the male.

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[1] *Mittheilung vom Physiolog. Laborat. des Carol. Med Chir. Inst. in Stockholm*, 1886; *Bihang vidk. Svenska Set. Akad. Handlingar*, Band ii., No. 2, June 6th, 1885.

The Influence of the Nervous System.—Ranvier's experiment consisted in ligaturing the vena cava between the spermatic and ilio-lumbar trunks. This operation and that of ligature of the femoral and iliac veins is commonly considered by clinicians to be necessarily a fatal obstruction and the source of intense œdema, even in cases where the vessel walls are healthy. No œdema occurs in dogs with this profound venous stagnation, unless as Ranvier showed, section of the vasomotor nerve fibres is superadded. In an animal so experimented on, very marked œdema is produced in the right leg in which the sciatic nerve was divided; whereas the left leg remained free from it, although, of course, the seat of equal stagnation. As regards the accuracy of Ranvier's dictum, which has been adversely criticised by Sotnitschewsky, it ought here to be said that of twelve such experiments we have seen Ranvier's result in nine. There is no doubt, therefore, that, as Ranvier stated, in dogs this combination of factors produces œdema. In cats and rabbits, as Sotnitschewsky[2] points out truly, we find the phenomenon is not nearly so marked. The actuality of the œdema thus evoked is well shown by dissection; a rapid dissection of the ankle region exhibits well the infiltration of the loose tissues about the tendo Achillis, and another, similarly prepared, the distension of the areolar spaces and separation of the component fibres.

The Chemical Condition of the Blood.—The late Dr. Wooldridge was the first to show that the condition of the albuminoids of the blood, especially the fibrinogens, could be profoundly altered by the injection into the circulation of certain other albuminoids which he termed *tissue fibrinogens.* The clinical action of these substances is to produce a twofold effect, namely (1) intravascular clotting; (2) a negative phase, namely, non-coagulability of such blood as may have escaped clotting. A small dose of such albuminoids, he discovered, led to the occurrence of œdema or dropsy, and extravasation of red blood corpuscles, when the altered blood was circulating through a district of tissue in which the blood vessels were moderately distended. Thus, if the femoral vein be tied, no œdema follows, but if Wooldridge's tissue fibrinogen be concurrently injected, then, as is shown in our experiments, the occurrence of œdema is very obvious. In this com-

[2] *Virchow's Archiv*, Bd. 57, p. 85.

bination of factors again, as in Ranvier's experiments, we are dealing with the vessel wall on the assumption that it is healthy and unimpaired. Now, as Wooldridge first showed, the disruption of the normal relation between the circulating living plasma and the vessel wall is not only a point of profound physiological importance, but is also relatively readily brought about by the injection of the substances termed by him "tissue fibrinogens."

The Relation of the Vessel Wall to the Blood within it.—We would venture in this sketch to allude to the behaviour of endothelium when it is the seat of pathological transudation. Arnold showed long ago that the stigmata and pseudostomata, as described by Dybkowsky, Schweiggerseidel, Cohnheim, Klein, and Sanderson, and a host of observers both previously and subsequently, are definitely increased in size when the influence of œdema or of exudation exciting agencies is brought to bear on the vessel. In animals in which, owing to the injection of the tissue fibrinogen, thrombosis and transudation were in active devolopment, the epithelial covering of the pulmonary pleura showed very marked pseudostomata.

Cellular Secretory Action.—It is impossible to conclude even a sketch of this kind without reference to Heidenhain's view of the secretory action of the endothelial cells of the blood-vessel walls, and probably also of the connective tissue corpuscles. We have as yet no new facts on this subject to offer; but we would refer to the table of points which must be investigated, to suggest if possible the way in which the fruitful suggestions of Heidenhain should be followed out. Mr. White has very kindly agreed to pursue the research so far as the changes in the blood and lymph vessel walls are concerned. It would be very gratifying if possibly concomitant investigation could be commenced on the various lines not at present in the hands of physiologists and pathologists, so that the elucidation of this important subject might be substantially pushed forward in relatively a short time.

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REMARKS

ON THE

FUNCTION OF THE THYROID GLAND:

A CRITICAL AND HISTORICAL REVIEW[1]

The Theories which have been Propounded concerning the Thyroid Gland.

In the history of every discovery in physiology or pathology we usually have to wade through the writings of a wearisome number of authors who are ready to occupy space and time in constructing theories as to the probable use or function of an organ without contributing any fact or definite observation to the subject, and that of the thyroid gland affords no exception to this rule. But there is a special point in the hypotheses concerning the present question, only applied to other organs or tissues in the dark ages of medicine, and that is the contention as to whether the thyroid gland has any function at all (Prochaska)[2] or serves any useful purpose to the economy.

It is universally recognised that: (1) The various organs of the body possess a different value to the economy in different classes of animals and at different ages of the same class or species. (2) If an organ be of importance, then its removal will be followed by constitutional disturbance (subject to the conditions mentioned in (1)) proportionate to the completeness of the loss of the function of the organ. With extremely few exceptions, the results of the investigations of the

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[1] A German version of this paper was published in *Virchow's Festschrift*, 1891. I have given the references in full in that publication, but considerations of space forbid their reproduction here.

[2] For example, such a classical work as Leisring and Müller's dismisses the subject in a few words, saying that the gland is not known to possess any function, but that recently (*sic*) the idea of its being a regulator of the cerebral circulation has been suggested.

authors I have consulted show that thus tested the thyroid gland is a structure of importance to the economy and that that importance varies in accordance with the principles stated in (1).

Those who deny that the thyroid gland possesses any importance, or that the symptoms evoked by its removal are due to the loss of its functional activity are Bardeleben, Cambria, Drobnick, Gibson (?), Kaufmann, Munk, Philipeaux, Tauber.

Bardeleben made three experiments in three dogs, of which one gave the usual positive result (*vide infra*). The negative cases, however, were not examined for accessory glands, and consequently cannot be regarded as of weight. Cambria stated that no constitutional disturbance followed removal of the thyroid gland. As however he followed the instructions given by Kaufmann (see below), he probably did not remove the thyroid, but the submaxillary glands, and the negative result of his work is consequently easily understood. Drobnick repeated Munk's experiments in eight dogs, of which three survived. Being, as he admits, for some reason unable to perform the operation aseptically, he naturally was led to believe that irritation of the nerves in the neck was the cause of the cachexia thyroidectomica (*vide infra*). Kaufmann bitterly attacked the views of Schiff and others, and stated that removal of the thyroid glands produces no constitutional disturbance. As, however, it is evident that he removed the submaxillary glands instead, his statement, as it is founded on an erroneous experiment, cannot be accepted. Munk, in his first publication, stated that although his own experiments showed complete and abrupt thyroidectomy in dogs to be almost invariably accompanied by fatal constitutional disturbance, nevertheless in his opinion this was not caused by loss of the function of the thyroid gland, but by certain (indefinite) injuries to the surrounding parts. In his second paper it appeared that these injuries were supposed by him to be lesions of the nerves in the neck, that is, the laryngeal nerves and the vago-sympathetic trunk. This idea that the symptoms might remotely have been thus produced occurred also naturally to the minds of the earliest experimenters. Schiff had directly examined the nerves in his researches, and I myself had carried out,[3] three years before Munk's publication, microscopic investigation of the nerves in my experiments, and had shown that when the thyroidectomy was properly performed, and duly followed by the characteristic symptoms the nerves nevertheless remained quite uninjured. Drobnick, in his experiments, also stated that he found the nerves involved in the scar tissue, which was not unlikely when the fallacies of his septic method are considered. Before Munk and Drobnick's publications, however, Baumgärtner had propounded the same view, and it was then repeatedly put forward (*vide* Billroth, etc.). For many years in England the symptoms of myxœdema had been attributed to lesions of the sympathetic. In consequence of the prevalence of this theory numerous investigators made special experiments on the point.

Munk states that by injecting croton oil into the capsular

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[3] My original publication, *in extenso* in the BRITISH MEDICAL JOURNAL in 1885, was evidently not known to Munk or to the large majority of my fellow workers abroad until recently.

tissue of the gland he obtained results similar to those of thyroidectomy, though differing in some respects from its characteristic phenomena. As, however, he undoubtedly complicated his experiment by, in some cases, injuring the gland itself seriously by the injections, the mixed result obtained by him, and quoted in support of his theory, is, in truth, only a corroboration of the views he opposes; and his experiment, repeated by Kemperdick, gave equally indeterminate results bearing the same interpretation.

Properly to test the point, a very thorough series of experiments was carried out by Ewald, Fano, Fuhr, Herzen, Carle, and Weil, and a few observations were made by Breisacher. In these experiments not merely the special glandular nerves derived from the sympathetic observed by Liebrecht and others, but also the trunks of the laryngeal nerves and even the vago-sympathetic trunk were subjected to every conceivable form of irritation by extensive traumatism, septic inflammation, even by direct inoculation of septic microbes, chemical irritation, electrical excitation—all producing intensely the conditions supposed by Munk to cause the cachexia thyroidectomica, but with absolutely no result. Finally, other observers have examined the condition of the nerves after thyroidectomy, and have found them uninjured. This has been done by Schiff, Fuhr, von Eisselsberg, Ewald, Loeb, and myself. The weight of evidence is so obviously against the view that the cachexia and acute symptoms following thyroidectomy are evoked as the result of irritation of the nerves in the neck, that it is now never seriously advocated, with the few exceptions before named; and the view that the thyroid gland is of some functional value, and not an "indifferent organ" (Bollinger), prevails.

Philipeaux stated that he removed completely the thyroid glands in four dogs 1 year old, and that a month later they showed no symptom. The observations of Tizzoni, Ughetti, Alonzo, among others, indicate that even in dogs a month or six weeks is too short for observation, and that at the end even of several—for example, seven to nine—months dogs have shown the fatal cachexia. In any case, moreover, in view of the immense number of positive results on dogs by so many investigators, these four negative observations are difficult to understand. Tauber made the remarkable statement that in an extremely large percentage—about 66 per cent.—of cases, he could find no thyroid gland at all in his animals.[4] This is so completely at variance with the observations of every other observer that his work cannot be accepted.

Theories of Function.

We have occupied sufficient space and time in the consideration of this very fundamental question, and must turn at once to discuss what theories have been formed as to the true function and importance of the gland. The theoretical modes of regarding its duties may be enumerated as follows:

1. That it is for the purpose of preserving the contour of the neck. 2. That it acts as a mechanical cushion to protect the important vessels and nerves from compression effects exerted by the contracting muscles. 3. That it acts mechanically to support the larynx and improve the voice. 4. That it acts mechanically, and protectively causes anæmia of the

[4] The account is so imperfect that it is not stated what kind of animal; possibly they were rabbits.

brain, etc. 5. That it acts mechanically, and protecctively prevents anæmia of the brain, etc. 6. That it manufactures some substance specially necessary to the integrity and proper functional activity of the central nervous system. 7. That it is directly a blood forming organ. 8. That it is indirectly a blood-forming organ. 9. That it plays a special part in the metabolism of the sexual organs. 10. That it modifies or destroys substances which, circulating in the blood, are harmful to the general economy. *Corollary.*—That it secretes some substance useful to the general metabolism of the body.

Passing over the first of these, a teleological theory originated by Wharton, we turn to the second, which was advocated by Luschka; but since not only is there no proof forthcoming in support of it, but also the experience of thyroidectomy directly negatives it, we may proceed to the third hypothesis, which, though supported by Boerhaave, Martyn, and Merkel, is nevertheless so directly contradicted by every observation of extirpation—hundreds of which have now been performed—as to call for no further discussion.

The next views which I shall consider are those which have been put forward by the anatomists, and it is a striking comment on the fallacy into which an observer is easily led if he ventures to argue from structural details alone as to the function of an organ, unaided by the only true method of inquiry, namely, experiment, that the anatomists are divided into two exactly opposite schools on this very point. One party believes that the thyroid acts mechanically to produce anæmia of the brain either by compressing the carotid arteries—Guyon; or, as a diverticulum of part of the blood stream—Rush, Waldeyer, Grashey. The other party, the opponents of this view and supporters of the fifth hypothesis—Schrager, Meuli, Liebermeister—believe that the duty of the gland is to prevent anæmia of the brain. Even the swelling of the gland in the recumbent position, which is put forward by the supporters of the fourth hypothesis, is claimed by their opponents as favouring their own view. It is very strange that so much should have been written and argued upon these fourth and fifth hypotheses without any of the authors testing their worth by simple experiment, which would have at once settled the matter.

Even the most recent anatomists, who have devoted attention to it, namely, Waldeyer, Staehel, Zeiss, etc., have trusted only to the revelations of structure, and in so doing have laid themselves open to the successful attack by the same weapons of a representative of the opposite anatomical camp, namely, Rüdinger. A corollary to the anatomical views is the theory of Forneris, who considered that the gland swelled during sleep, with the evolution of which condition he considered it to be connected.

All the hypotheses, therefore, which merely rest on a point of general import, such as the vascularity of the gland, etc., should claim no further consideration.

The sixth hypothesis, namely, that the thyroid gland manufactures some substance specially required for the proper nutrition and functional activity of the nervous system, is one which has been advanced by some authors—John Simon, Weil, Sanguirico, with Canalis—but is not strongly supported. The fact that the nervous system suffers so prominently in the cachexia thyroidectomica is no proof in favour of this restricted creed of the function of the gland; it is only one expression of the general disturbance of metabolism caused by loss of the thyroid tissue.

The seventh hypothesis has long been in favour, owing to

the theoretical hæmopoietic action of the gland having only of late years been more defined. In fact it has usually been confused with the eighth hypothesis, of which more will be said immediately. Direct hæmopoiesis may be imagined to occur (*a*) in the manufacture of leucocytes, (*b*) of red corpuscles, (*c*) of the constituents of the plasma.

As yet the hæmopoietic influence of the gland has only been investigated as far as (*a*) and (*b*) are concerned. The first observations, those of Crede, Zesas, and others showed that consequent upon the loss of the spleen the thyroid gland underwent hypertrophic changes or *vice versâ*, upon which the disappearance of previous leucocytosis was noted. All the experimental observers who have witnessed the cachexia thyroidectomica have noted the remarkable anæmia characteristic of this condition. I myself, in 1884, devoted special attention to this subject, and found that in monkeys the red blood corpuscles diminished steadily from the time of the thyroidectomy for a fortnight, and then reached an oligæmic equilibrium which persisted to death. The leucocytes, on the other hand, became treble in number, but when the oligæmic condition of the red corpuscles began to be marked the leucocytes steadily diminished to below normal at death. In accord with the observations of Crede and Zesas on man, I found that in some cases of thyroidectomy in monkeys the spleen was also enlarged, but this fact has been only exceptionally observed in the carnivora, although a very large number of experiments have been performed. For a further discussion of the vicarious action of the spleen and thyroid gland as regards hæmopoiesis I must for brevity refer to the writings of Zesas.

There remains a line of research which has not to my knowledge been followed up; that is the question of the presence of lymphoid tissue and the enumeration of the leucocytes in the thyroid artery and veins respectively. In 1886 I showed that in addition to the embryonic gland tissue described by Baber and Wölfler there was definite lymphoid tissue of a distinctly splenic character; further, that leucocytes were present in notably greater proportion in the veins than in the arteries, and that this proportion was greater than that to be found in the vessels of the limbs.

There is no evidence that the thyroid gland is directly hæmopoietic as regards the red corpuscles or the blood plasma, but Kohlrausch has found that in the acini are bodies closely resembling blood plates. This introduces us at once to the eighth hypothesis, according to which the thyroid gland is indirectly hæmopoietic. It has always seemed to me obvious that its influence must be exerted first on the chemical metabolism, especially of the albuminoid constituents of the blood, and that while there was no positive evidence that the normal effect is a constructive one, it is perfectly clear that the absence of the gland must very markedly alter the constitution of the blood, and so, indirectly, hæmopoiesis must be dependent on the integrity of the thyroid. This is a point of considerable importance in view of the fact that all observers who have examined the condition of the blood after thyroidectomy have found it notably altered in its constitution and function, even apart from the changes in the corpuscles already referred to. (Sanguirico, with Canalis.)

The changes in the blood apart from the alteration in the numbers in the corpuscles are as follows: (*a*) Increased

venosity (all observers, especially Herzen, Hofrichter, and Rogowitsch). (*b*) Great diminution[5] in the amount of oxygen (Albertoni and Tizzoni) which may in the arterial blood fall below the normal proportion in the veins. This condition has been termed by Herzen "anoxyæmia." (The connection of this condition[6] of the blood with the activity of the respiratory centre is given below). (*c*) Presence of abnormal constituents of the plasma. Halliburton has found mucin in the blood of monkeys on which I had performed thyroidectomy.

It requires no insistance to point out that such changes in the blood gravely altering its constitution and functional activity must evoke a considerable degree of anæmia both by destructive changes in the fluid itself and by the effect which it, thus altered, necessarily exerts on the blood-forming tissues—for example, marrow.

The statement of these points relating to the influence of the thyroid gland as regards hæmopoiesis will serve, I trust, to make clearer the position I have always held, and which Professor Virchow has done me the honour to criticise. The final solution of the questions raised will be rendered easy by future researches.

The ninth hypothesis which directly connects the function of the gland with the functions of the female sexual organs is many centuries old. Of late years the subject has been so carefully considered by Freund[7] in its chief bearings that it is hardly necessary for me here to do more than point out how the truth of the conjunction of the functional activities of these parts is confirmed by the far greater liability of the female sex to suffer from myxœdema. The harmony between the two sets of organs is evinced by the enlargement of the thyroid occurring when active changes happen in the sexual organs. What is the nature of the change which requires the increased activity of the thyroid is not yet known, but that such a need should arise is comprehensible from the altered condition of the blood in pregnancy and menstruation. The widespread alterations in metabolism, which are frequently noted in these conditions, would naturally create a necessity for increased activity in a metabolist organ like the thyroid. As an indirect confirmation of the relationship, Schönlein shows that there are two maxima for the appearance of goître —namely, the development of puberty and of senile involution respectively.

There remains the tenth hypothesis, which is the most important of all, and the demonstration of which is necessary to the proof that the thyroid gland is the active agency in metabolism that has been suggested in these pages. The task before us is first to review the facts accumulated during the last decade in the investigation of the following conditions—first, thyroidectomy in birds, rodents, ruminants, solipedes, carnivora, monkeys, men, and its relation to (1) myxœdema, (2) cretinism; and, secondly, to summarise the general level of knowledge thus attained for the purpose of categorically stating the present position of the subject.

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[5] Michelson and Tarchanoff say that the whole gas exchange of oxygen and carbonic acid is increased; according to the latter to three times the normal amount.

[6] Pisenti and Viola consider that the secretion of the thyroid may by being constantly supplied to the blood prevent the development therein of some toxic product, which poisons the system if the gland be removed.

[7] For the special literature of this necessarily indeterminate point consult Freund's valuable paper.

Nature of Thyroid Tissue.

We must preface the demonstration of what happens when the function of the thyroid glands is lost by some consideration of the circumstances under which the normal gland tissue exists in functional activity. Having already alluded to the hæmopoietic action of thyroid tissue, and having shown the error of believing that its rich blood supply merely suggests a mechanical appendage to the cerebral circulation, we are able to discuss its proper glandular structure. It was suggested by Morgagni and some of the older writers that the thyroid secreted a colloidal or glairy substance. These hypothetical ideas, however, were worthless until King showed that gentle pressure on the lobes of the gland caused the contents of the gland acini or vesicles to flow into the peripheral lymphatics. After he had thus filled the lymphatics, he coagulated their contents *in situ*, and thus readily demonstrated the mode of exit of the secretion, which he thus recognised the colloidal product of the gland to be. Boéchat and Baber first showed microscopically that the periacinous lymphatics contained the colloidal material seen in the acini, and thus anatomically confirmed the experimental demonstration of King as to the connection between these cavities. I also found the same condition constantly to exist, and determined the obvious truth of Baber's view that the acinous epithelium was a true secretory gland tissue which separated the colloidal material from the blood, and that this found its way into the circulation by means of the lymphatics. Quite recently the subject has again received attention from Langendorff, Biondi, and Kohlrausch, all of whom have reconfirmed these views. They have also acceded to the opinion that the vesicles in part intercommunicate, and Langendorff has dwelt particularly on the secretory character of the epithelium, and especially on the intimate connection between the protoplasm of the cell and the colloid material. The secretory character of the epithelium has been further exhibited by the experiments of Wyss, who, inspired by Gaule, injected pilocarpin with the result of increasing remarkably the secretion of the colloidal substance, as well as of producing extra colloidal change, extension, etc., in the epithelial cells, after the toxic action of the drug had become well established.

As to the colloidal secretion of the gland, that was shown in 1826 by Babington to be albuminous and not mucin. The same opinion was formed by Gorup Besanez, who showed that, unlike mucin, it was soluble in acetic acid. Langendorff's micro-chemical experiments also yielded the same facts. Besides various forms of alkali-albumin, water, salts, etc., according to Moscatelli, paralactic acid must be specially mentioned among its constituents. The same substance has been also found by Hirschler in those lymph glands which receive lymph from the thyroid gland.

The physiological influence of the secretion has also been directly investigated, first by Ewald, who found that the juice expressed from the thyroid gland of a dog produced in another such animal coma after three hours, and, further, that the extract from other animals was not so toxic at all. I repeated the experiment with the gland of the sheep, and obtained only negative results, as also was the case with Alonzo's experiments. Langendorff noted drowsiness to fol-

low such injections in rabbits. As I pointed out some years ago, this experiment is complicated by the presence of tissue fibrinogens (Wooldridge), which are very toxic. In accordance with this, it is important to note that several experimenters (Langendorff, etc.) have seen intravascular clotting to occur as the result of their injections. Wagner finds that injections of mucin determine in cats tremors and tetanoid spasms resembling those of the cachexia thyroidectomica. Closely connected with this point is one which is discussed on page 219, namely, the effects of injecting the secretion of the gland in animals from whom the glands have been removed, and at the same time the source and mode of improvement in myxœdema caused by transplantation of gland tissue.

Function of the Thyroid.

We must conclude, it seems to me, that the thyroid gland is a structure essentially connected with the metabolism of the blood and tissues; that in fulfilment of its functions it is hæmopoietic both directly and indirectly, and that it forms, that is, secretes from the blood a colloidal substance, which is transmitted *viâ* the lymphatics from the acini of the gland to the circulation.

Importance of Thyroid Tissue to the Economy.

The relative importance of a gland in its service of the needs of the organism is well shown by its developmental history. This is particularly true of the thyroid gland in both its normal physiological relations, and under morbid conditions. I have myself found that in the human fœtus the gland tubes, or rather cylinders of epithelium, during the interval from the sixth to the eighth month commence their secretory function. Huschke showed that in proportion to the body weight the gland was heaviest at birth, and notably diminished towards the end of life. Not only is the mass of the gland greater in early life, but histological research (Canalis and Tizzoni) shows that whereas karyokinetic changes are very frequently to be seen in the epithelial cells of the glandular acini in young animals, they are correspondingly very rare in the acinous epithelium of old individuals.

In strict accord with these proportional estimates are (1) the anatomical degenerative changes which occur in consequence of senility and (2) the anatomical changes witnessed in general wasting diseases in which the metabolism of the body is generally lowered. (1) Those alterations which are due to old age are widely known—namely, fibrocystic degeneration, etc.—but have been well described by Hale White and Pilliet, who find cystic degeneration, interstitial cirrhosis, great diminution of the colloidal secretion, and retrogressive changes in the glandular epithelium, the acini being filled with broken-down *débris* of the cells. (2) Defaucamberge, working under Cornil, has found that in phthisis the secretory activity of the gland is very notably decreased, and consequently the colloidal substance disappears from the acini, which come to resemble the epithelial cylinders of the embryonic stage.

The thyroid gland, therefore, is in functional activity before birth, and is of special metabolic importance in early extra-uterine life, while its value falls as the general vital processes decrease. This position is finally confirmed by the crucial experiments of pathology as follows:—

(*a*) Experimental thyroidectomy is very much more fatal to young animals than to adults. This I have found to be markedly so in monkeys; Schiff, Wagner, Ewald, and others in the carnivora. Cooper's two experiments are the only ones to my knowledge which oppose this general conclusion, and they must be considered to be imperfect, since the animals were not kept for a sufficiently long period nor examined for accessory glands. Sanguirico and Orecchia state that in ruminants the removal of the gland in 3 lambs was not followed by the cachexia. Judging from my own experience of adult sheep, I do not think that in these cases the animals were observed for a sufficient length of time. It would, therefore, be very advisable that the experiments should be repeated and largely extended. Conversely, Hegar, Simon, and myself have found that removal of the gland in aged carnivorous animals is not followed by the usual rapid cachexia.

(*b*) Cachexia strumipriva has been found by all observers to occur with far greater frequency when the thyroidectomy has been performed in young individuals. This is well shown in the accompanying table which is copied from Bourneville and Bricon's valuable paper on Sporadic Cretinism:—

Liability to Cachexia Strumipriva after Total Thyroidectomy.

Age.	Cases observed.
10 to 20 years	... 18
20 ,, 30 ,, ...	... 14
30 ,, 40 ,, ...	... 3
40 ,, 50 ,, ...	... 2
50 ,, 60 ,, ...	... 1
60 ,, 70 ,, ...	... 1

This table shows that the liability to constitutional disturbance following the loss of the function of the thyroid gland is extremely marked in early life, and almost abruptly ceases at about the 30th year. The observations of anthropologists have for a long time tended to show conclusively that active growth—that is, increase—also ceases at the 30th year. The concordance of these two facts strikingly illustrates the bearing of the gland's function on the general vital activity. Kocher, who has had so large an experience, is of the opinion that total thyroidectomy performed before puberty will inevitably be followed by the cachexia.

(*c*) Intrauterine cretinism is now (Virchow, Barlow, Shattock, Eberth, Bowlby, Sutton) well recognised, although for a long time it was described under the title of fœtal rickets. In this condition either the thyroid gland does not develop normally or it undergoes atrophic changes, so that at the time of birth usually not a trace of it is to be found, very rarely it has been described as normal, but no microscopical examination made. Under these circumstances the cretinic and myxœdematous cachexia is excessively advanced during the intrauterine life of the fœtus, so that it is almost invariably born dead.

(*d*) To this may be added the well known fact that in countries where cretinism is relatively rare—for example, England—there occurs a myxœdematous form which follows morbid changes in the thyroid gland in children, producing what is spoken of as "sporadic cretinism" or "*idiotie pachydermique*" (Bourneville and Bricon). In the present paper, however, I cannot deal with these conditions except so far as

they illustrate points like the present, emphasising the apparent importance of the gland in early life.

The conclusion therefore affirmed above concerning the relative value of the gland according to the age of the individual need not be further insisted upon.

The Distribution of Thyroid Tissue in the Body and its Relation to the Pituitary Body.

The occurrence of thyroid tissue in other parts than the lobes of the gland in front of the trachea is, as will be subsequently seen, a matter of far more than embryological interest, and the coexistence of the pituitary body may conveniently be considered at the same time. The development of the thyroid gland proper can not be entered upon here, but not only are the position, early appearance and relations of the gland in the embryonic life of the higher animals evidence of importance, but as shown by Julin and others the same appears to be true of the lower vertebrates; for example the Ammocœtes.

The principal fact, however, of importance to the present question is the existence[8] of additional masses of thyroid tissue or accessory thyroid glands as these have been termed. Since Gruber described the proportional frequency of accessory glands in man, numerous authors (Callender, Bruch, Kadyi, Zuckerkandl, Madelung, Streckeisen, Wolf and Porta) have considered the subject in all its anatomical bearings and collected the literature upon it. This last duty has been specially carefully performed by Madelung and Semon. Briefly summarised, these accessory glands may be grouped in man as follows:

Region of the Hyoid Bone: *Supra-hyoideal*, *Præ-hyoideal*, *Infrahyoideal*.—Of these the infra-hyoideal gland has long been known as the middle or pyramidal lobe of the thyroid body. This Callender showed to be really a free mass of tissue, and in 2 per cent. of the cases examined by Gruber, he regarded it as a superior accessory gland. Streckeisen subdivides the remaining two kinds thus: (1) Præ-hyoideal, (2) supra-hyoideal, (3) epihyoideal, and (4) infrahyoideal, but these were not only found in man.

Region of the Thyroid Gland.—Porta, Gruber, and Bruch found accessory glands termed lateral or posterior either under or behind the lateral lobes of the thyroid body and the gullet, and these have been repeatedly found enlarged and removed by operation (Wolf, Barker).

Region of the Aorta and Great Vessels.—In the dog, Piana stated that accessory thyroid tissue was present situated close to the aortic arch in 66 per cent. of all cases examined by him. Ewald similarly found that in every one of five dogs which suffered from goître there happened to be also enlarged aortic thyroid glands. Other authors, Wölfler, Wagner, and Carle have also determined the existence and relative constancy of these accessory glands, and it will be remembered that according to Kölliker the thyroid gland in its development commences close to the bulbus aortæ (in the rabbit). In the carnivora accessory thyroid glands have been found in other situations (Fuhr, Autokratow). Munk states that although he has looked in general for accessory glands in animals, he has never found one.

As of course positive evidence must always outweigh negative evidence we nevertheless are compelled to conclude that accessory glands occur with notable frequency.

The bearing of all these facts will be seen further when the question of compensatory action of other tissues arises in cases where the thyroid is lost, but it seemed more proper to discuss the prevalence of this specialised tissue at the moment when the general importance of the gland as a metabolising organ was under consideration,

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[8] Von Eisselsberg could not detect any accessory glands in the cat.

The Pituitary Body.

Attention must now be directed to the pituitary body, inasmuch as from the development of the anterior lobe, as well as from its structure, it is evidently closely allied to the thyroid body, and, like it, plays probably a more important part in the economy than has previously been attributed to it.

The description of the development and histology of the pituitary body (anterior lobe), which is given in most textbooks, has been notably supplemented by several authors, especially Rogowitsch, Pisenti and Viola. From these researches it is obvious that the anterior lobe of the pituitary body is an epithelial structure, the cells of which are arranged cylindrically, and that there is a series of lacunar spaces surrounding them which, together with the blood vessels contain, in the normal state, colloidal material.

As yet but little research has been directed to the relation between the thyroid and pituitary bodies, apart from similarities of structure, but there is some direct evidence on this point, and what there is goes to show that the pituitary body responds (in a compensatory manner (?)) when the thyroidal function is lowered. Thus Rogowitsch has found that after thyroidectomy in dogs the pituitary gland is swollen, and the cells become vacuolated and ultimately disintegrated the longer the animal survives the thyroidectomy. Finally, in sporadic cretinism, where the thyroid gland is lost, the pituitary body has been found to be enlarged (Bourneville and Bricon).

Indirect Evidence of the Importance of the Thyroid Gland.

In accordance with the well-known laws of gland physiology, the thyroid, upon loss of one lobe, shows compensatory hypertrophy of the other. This "hypertrophy" has been observed under different circumstances.

When Half the Whole Gland has been Removed.—Wagner was the first who recognised enlargement of one lobe to occur if that of the opposite side were removed. In the following year I confirmed his statements, but like subsequent investigators—von Eisselsberg, Breisacher, who also obtained the same result—I noticed that it did not always occur. It soon became evident to me that this inconstancy was apparently due to the variable condition of the animals so far as their constitutional state was concerned. Where the active metabolism of the tissues was lowered from any reason, and the animal neither grew nor increased in weight, the remaining lobe of the gland did not hypertrophy, but when the animal was not old at the time of operating and developed normally, then the thyroid tissue hypertrophied in an apparently parallel degree to the needs of the metabolism of the body. This view has been confirmed by the observations of von Eisselsberg, who found the hypertrophy only to occur in young individuals. There are many points, especially in regard to the histology of this hypertrophy, which are well worth of an extended study,[9] but the observations are too scanty to admit of further consideration in detail.

Hypertrophy of Accessory Thyroid Glands.—It has been ob-

[9] I very greatly regret that the details of the splendid work by Professor Halsted and Professor Welch are not available for this report I anticipate much will be learnt from their researches on this very question of "hypertrophy."

served after complete thyroidectomy in man that other islands of thyroid tissue became enlarged, and that whereas temporary symptoms of cachexia (Reverdin) may appear, they improve in proportion apparently to the degree of swelling of the accessory thyroid glands. In one interesting case (Shattock), destruction of the thyroid by a neoplasm led apparently to hypertrophy of an accessory thyroid gland. Following closely on the evidence afforded by hypertrophy of the remaining thyroid tissue when part is lost is the remarkable series of experiments on transplantation of thyroid tissue commenced by Schiff, and so thoroughly elaborated by von Eisselsberg. Schiff found in the dog that transplantation (intraperitoneally) of the healthy gland shortly before the operation of thyroidectomy was sufficient to protect the animals from the fatal cachexia, although they appear to have constantly suffered from the tetany. Carle found that transplantation a week after the thyroidectomy was inefficient to ward off the cachexia. This experiment repeated a few times by other investigators, however, did not yield the same positive result until von Eisselsberg renewed the research on a larger scale, and found that in cats, if the transplanted gland underwent atrophy and degeneration, the usual cachexia supervened. If, on the other hand, the gland became properly vascularised and resumed its functional activity, then the cachexia did not show itself. This very conclusive evidence suggested to me the advisability of introducing the practice of transplantation as a rational treatment of myxœdema and cretinism. I was not aware until some months later, by the subsequent publication of Bircher, that this had already been performed by him as treatment of cachexia strumipriva, and I afterwards learnt, through the kindness of Professor Kocher, that he had commenced it as long ago as 1883. In France it has been taken up, and operations by Lannelongue, Merklen and Walther, Bettencourt and Serrano have been performed in myxœdema and sporadic cretinism. The sum of all these operations is unquestionably a notable improvement in the patients and amelioration of the symptoms in those cases where the grafted gland survived.

Amount of Gland which in the Carnivora must be left for Functional Purposes.—In accordance with what has been said, it will be recognised that a valuable point in connection with this branch of the subject is the question as to how much of the gland is necessary to meet the needs of the organism. The statements of investigators (Colzi, von Eisselsberg, Fuhr, Sanguirico, with Canalis, Weil) are pretty close, and show that in dogs and cats there must be at least one-third, or in some cases one-fourth of the gland left to prevent the onset of the fatal cachexia. It follows from what I suggested above that the value of this remnant will be very different according to the constitutional state of the animal. Coupled directly with this point of residual portions of thyroid tissue being available for the metabolic necessities is the question whether gradual extinction of the gland (thus anticipating the effect of senility) could be accomplished without causing the fatal cachexia. Schiff first attempted this by successive extirpations at considerable intervals in dogs, but he found that as a rule the procedure was only occasionally survived. In his and all the various methods of gradual extinction of the thyroid gland, a remarkably constant feature appears, and that is the outbreak of many of the initial symptoms of the

cachexia, that is, tetany, hebetude, etc. These are developed (Schiff, Colzi, Fuhr, Fano, with Zanda) in proportion to the destruction of the gland tissue, and disappear when the metabolic equilibrium is regained, often by hypertrophy of accessory tissue. Colzi and Fano (with Zanda) found, further, that transfusion of healthy blood caused these preliminary symptoms to diminish. Munk stated that if the gland were isolated, shelled out of its bed, but left *in situ* with the vessels ligatured and primary union secured, the animal would probably recover, but that if suppuration occurred, as seems to have happened in the large majority of his cases, death ensued. His experiment has been repeated, however, by several observers—Weil, von Eisselsberg, Fano, Ewald—who state, on the contrary, that the effects are the same as thyroidectomy. Munk's own description, moreover, shows that where the nutrition of the gland substance and contents was completely destroyed by the operation, the cachexia inevitably followed, and the same conclusion is arrived at by the abovementioned investigators, who have repeated his experiment, as well as by Tarchanoff, who ligatured all the vessels supplying the gland. A further point is raised by these experiments, namely, the temporary warding off of the unfavourable symptoms by the animal absorbing the secretion, yet remaining available in the residual gland structure. This was the view taken by Schiff of his transplantation experiments. A positive observation in its favour is the result of the experiments conducted by Vassale on nine dogs. This author found that if, immediately after thyroidectomy, the expressed juice and secretion of the glands were injected into the animal, the cachexia was thereby considerably diminished, that is, the venosity of the blood improved, as also the conjunctivitis, etc.[10] Von Eisselsberg, however, saw no such improvement in cats similarly treated.

Evidence of Active Growth, that is, Regeneration of Thyroid Tissue when this has been in part removed.—Active growth or regeneration on the part of the thyroid tissue, if it existed, would be in support of the opinion that its integrity is a metabolic necessity. As a matter of fact, the true thyroid glandular tissue does show a strong tendency to regeneration, especially in the peripheral regions (*cf.* also Wölfler). Canalis, Ribbert, and Neumeister have found that in dogs and rabbits the removal of portions of the gland was followed in a few (two to three) days by, first, the appearance of mitotic figures in the epithelial cells of the nearest acini; and, secondly, the growth of the epithelium as cylinder masses, which subsequently formed new acini in the supporting tissue of the scar.

Summary.—To sum up the indirect facts, we see that they afford very weighty evidence in favour of the view that the thyroid is in truth the important origin of metabolic influence that the general results of thyroidectomy would lead us to believe it to be.

The Effects of Thyroidectomy.

I have thus far been compelled to assume what is a matter of common knowledge, namely, that the extirpation of the

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[10] Compare the gratifying results obtained by Dr. G. Murray in treating myxœdema by this method. British Medical Journal, October 10th, 1891, p. 796.

thyroid tissue in a healthy animal will, under certain circumstances, produce a remarkable and fatal series of symptoms which have beeen spoken of as "cachexia strumipriva," or "cachexia thyroidectomica," etc.

These conditioning circumstances and the details of the cachexia must now be briefly recounted. Of these, the first and the most important, fundamentally, is the question of the class of the animal, inasmuch as the physiological value of the gland differs very considerably according to the species employed.

Effect of Class of Animal upon the consequences of Thyroidectomy.

Birds, Rodents, Ruminants, etc.—In the first place, it appears that thyroidectomy in birds is never accompanied by cachexia. This has been established in chickens by Allara, and very carefully by Ewald and Rockwell in pigeons. It is possible, however, that duration of life after the operation may in these animals play the important part it does in some other orders. From his earliest experiments Schiff recognised that the rodents (rats and rabbits) differed from the carnivora so far as the effects of loss of the thyroid gland were concerned, and in his first publications he drew attention to this important fact. Philipeaux also found that no effect followed thyroidectomy in albino rats. In the same year Colzi demonstrated that the rodents did not show the cachexia, as also Rogowitsch, and later Albertoni and Tizzoni. I found myself that whereas the carnivora showed the cachexia in its most marked form, it was less marked in the monkey and absent in rabbits; however, the influence of duration after the operation has never been discounted in the case of rodents. On turning my attention to the ruminants, solipedes, and suidæ, I found that in the sheep in one case, after preliminary symptoms had shewed themselves, the animal survived a considerable interval of time—569 days—at the end of which exposure to cold determined the onset of the fatal symptoms.[11] Exactly the same was observed with a donkey, in which preliminary symptoms followed the loss of the gland for some weeks, and then, these having ameliorated, the fatal cachexia supervened after a long interval[12] of months when the animal was exposed to cold. In pigs observations by myself and by Munk have yielded negative results, but the animals were not observed for a sufficient length of time, the more especially as the gland in these animals is relatively small. Many years before von Rapp removed the thyroid from a goat, which was stated to have survived, but not watched for a long period. It has also long been known that the removal of goîtres in horses and mules is ultimately fatal. It is evident that many more experiments are very requisite in these larger animals, but so far as the positive results go the conclusion is obvious that certainly in the ruminants and solipedes the operation of thyroidectomy is followed by the usual fatal cachexia after an interval of many months.

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[11] The first sheep referred to on page 76 of the *Clinical Society Report* as surviving has since died—that is, more than three years after the thyroidectomy. Unfortunately its symptoms were very imperfectly observed. *Post-mortem* examination (without chemical examination) showed œdema of the lung, serous effusions, etc.

[12] If anything were wanting to demonstrate the fallacy in Munk's view that the cachexia thyroidectomica is due to injuries of the nerves in the neck it is the fact that in these large animals and in monkeys the symptoms are not well marked until the wound is absolutely healed, and the tissues perfectly quiescent, in some cases for months.

Man.—In man the observation of the sequence of events is, of course, not open to such accurate measurement. After the likeness of the symptoms of myxœdema to cretinism had been described by Gull, it was reserved for Ord to define clearly the existence of myxœdema, and to completely exhibit the disease in its general bearings anatomically as well as pathologically. He first determined the destructive changes in the thyroid and the profound alterations of the connective tissues. The treachery of clinical deductions is, of course, proverbial, but may naturally be less questioned in cases where persons in health, but for the inconvenience and distress of a goître, have been subjected to complete thyroidectomy. But here also opportunity of fallacy is present, inasmuch as the object of the operator, being in every case to do no more than is absolutely necessary, it has been most usual for the extirpation to be incomplete (Wölfler, Semon, Biondi). Where total extirpation has unquestionably been performed, however, Kocher thinks that the cachexia in greater or less degree infallibly supervenes. Reverdin, who first noted and fully described the occurrence of the cachexia in man, has shown that the statements as regards non-appearance of the symptoms are often due to imperfect observation; but of greater interest is the occurrence of cachectic symptoms and their disappearance concurrently with restoration of thyroid function by means of compensation. Reverdin has termed this *myxœdème fruste*, an expression which very fitly represents the arrest of the cachexia. Conversely several authors (Poncet, Niehans, Zesas, Schulthers, Lüning, and Occhini) have shown that partial operations on goîtres may occasionally initiate cachectic symptoms. The earlier facts of all authors, carefully summed up by Semon, showed that from one-third to one-fourth of so-called total thyroidectomy operations is followed by the cachexia. Doubtless with the spread of knowledge of the disease, and with opportunities of *post-mortem* examination, the real parallel between the operation and its consequences will be soon established.[13] Finally, it is sufficiently significant that no surgeon nowadays performs the operation of total extirpation except for malignant disease.

Classification.—If we now arrange the classes of animals in a line, we see that the following order is assumed:—

Consequences of Thyroidectomy.

No Cachexia.	Slowly Developed Cachexia.	Moderate but Certain Cachexia.	Severest Cachexia.
Birds Rodents	Ruminants Solipedes	Man Monkeys	Carnivora

From this arrangement it is obvious that the difference of class of animal is tantamount to saying difference of nutrition and metabolism, for obviously the animals which suffer most are flesh feeders, and those which suffer least are vegetable and grain feeders, while omnivorous animals take a more or less intermediate position. This broad and important generalisation has recently received unexpected confirmation. Being apparently unaware of much of the previous work on the subject, Breisacher, a pupil of Munk's, made fresh re-

[13] See the thorough investigations of Reverdin, Kocher, Bruns, Hoffa, and Stokes.

searches on the latter's theory that the cachexia was due to the "injuries" (*Schäden*) received by the nerves in the neck. It will be remembered that Munk laid much stress on the fact that if a dog in whom thyroidectomy had been performed were given lumps of meat the characteristic symptoms commenced, whereas if it were fed on milk the symptoms were delayed a little, and at any rate not excited. Munk adapted this observation to his theory by suggesting that the lumps of meat mechanically irritated the nerves during the passage down the gullet.

Effects of Food.—Breisacher found, however, that the dogs could swallow any number of lumps of meat provided the latter was thoroughly extracted by boiling. By this means of course all the extractives, etc., were removed such as are known to be toxic to rodents[14] (Kemmerich and Boguslowski), and which by this interesting observation were shown to be als toxic to carnivora whose metabolism was already disturbed by the loss of the thyroid gland. The final proof was afforded by feeding the dogs on the bouillon instead of milk, when the cachexia rapidly appeared. Although these facts are extremely clear, it is by no means settled, as Ewald remarks, whether after thyroidectomy it is the constituents of the food which are directly toxic or whether it is the disturbance of the chemical changes in the tissues which directly gives rise to the cachexia. This is a fertile field for future research.

Other Conditioning Circumstances.—Other conditioning circumstances have already been alluded to, namely, the influence of age, existence of accessory and residual tissue, and need not be further dwelt upon. Others still to be mentioned are previous state of nutrition and temperature. It is easy to understand that the former must be very important in influencing a general metabolic condition. Hence it is that a state of low nutrition before thyroidectomy leads to early and very severe cachexia. I have found this to be particularly the case in monkeys. The influence of temperature I have already discussed fully in the report of the Clinical Society, but I will return to the question directly in considering the changes in temperature after thyroidectomy.

Symptoms presented by all Classes of Animals after Total Thyroidectomy.

I do not propose to weary my readers with a detailed account of the symptoms of the cachexia thyroidectomica found in all animals, since they are given at length in the writings of Albertoni, Alonzo, Canalis, Colzi, von Eisselsberg, Ewald, Fano, Fick, Fuhr, Herzen, Hoffa, Horsley, Loeb, Mattei, Munk, Rogowitsch, Sanguirico, Schiff, Tizzoni, Ughetti, Wagner, Weil, von Wyss. Moreover, I have already arranged, in the report to the Clinical Society, the phenomena of the cachexia, and I see no reason to alter the views expressed therein as yet. Unfortunately the investigation of this subject in monkeys has only been taken up besides myself by Munk, and although, as I showed in the report above mentioned, his experiments,

[14] In one of Billroth's cases reported by von Eisselsberg the patient from having been a meat eater experienced an unconquerable aversion to it after the operation.

though not complete, nevertheless confirmed in more than the chief points my results, it would doubtless advance the science of the subject if someone with intimate knowledge of the cachexia and of these animals would renew the examination of the questions at issue. This is rendered the more desirable since the intensity of the cachexia is so different in various species that it is probable a thorough comparative research would throw much light on the general or so-called "constitutional" changes.

I will now review the facts ascertained concerning the chief groups of symptoms, and trace as far as possible their origin in the anatomical changes found *post mortem*.

Symptoms of Disorder of the Nervous System.

This group of symptoms has always attracted most attention, partly because the phases appear early and are well marked, but also because most research has been performed on the carnivora, which as a rule die too soon for the development of other changes. Dividing the symptoms, according to the method of Hughlings Jackson, into (1) those exhibiting over action and (2) those exhibiting want of action, the following is a brief summary of the observations:—

1. *Over-Action.*—The first symptom of over-action is fibrillar muscular tremor or twitching, resembling closely the disease called tetany (Schiff and all observers, *cf.* especially von Eisselsberg), and having perhaps a similar pathology. The individual contractions of the muscles I have found in monkeys to follow one another at the customary (according to Gowers and myself, see also Schäfer with myself, *Journal of Physiology*) rate of clonus, namely, 8 to 10 per second. Summation next occurs and tetanoid spasms ensue (Schiff and all observers), and finally rigidity and contracture. Similar tremors had long been known from the early observations of myxœdema, and I have seen the same in acute enlargement of the thyroid gland, while Marie with Charcot described them later in exophthalmic goître. In man, after thyroidectomy, von Eisselsberg has shown from Billroth's cases that, while tetany occurred 12 times in 53 cases of so-called "total" extirpation of goîtres, it never appeared once in 115 cases of partial extirpation.

2. *Want of Action.*—Coupled with the symptoms of over-action are those of want of action, which evince themselves as motor paralysis and anæsthesia. I have noted in the monkey that the toxæmic condition after thyroidectomy produces not infrequently functional neuroses—that is, epilepsy, hemiplegia, etc.—as does the parallel condition of anæmia.

Pathology and Morbid Anatomy.

The important question now arises, What are the pathology and morbid anatomy of these conditions?

Lower Centres Mainly Affected.—As regards pathology, Schiff showed that the tremors and spasms were not of peripheral origin, since section of the motor nerves arrested them. Peripheral changes (that is, neuritis) have been described by Albertoni and Tizzoni, but the experimental observation just referred to proved the seat of mischief to be central. After confirming the fact established by Schiff, I found that in monkeys ablation of the excitable, or so-called motor, cortex did not stop the tremors. Three years later Munk divided the

spinal cord in dogs, and found that the spasms continued. These observations all tend to show that the lowest centres are the source of the muscular twitchings and spasms. Possibly the higher centres (Herzen) are also in a state of discharge, since the whole central nervous system in advanced cases shows anatomical changes. These changes, primarily anæmia and œdema (Sanguirico and Canalis, Schiff, Horsley), vary according to both the intensity and duration of the symptoms. When very marked they have been described by Weiss as hyperæmia, by Rogowitsch as "encephalitis parenchymatosa," since he found in the cortex cerebri hyperæmia, exudation of leucocytes, and vacuolation of the nerve corpuscles.

Schultze and Schwarz, while not accepting this description, describe an exudation of leucocytes into the meninges of the upper part of the spinal cord. I have found that in the carnivora the appearances thus described are sometimes, but not constantly, to be found. Herzen and Löwenthal also observed vacuolation and atrophy of the large pyramidal corpuscles of the cortex cerebri in the lower limb area. But the direct effect of the cachexia has been measured by experiment in testing the functional activity of the nervous system. Schiff was the first to approach this question, and he investigated the effect of excitation of the so-called motor region, and found the excitability diminished.

Alteration of Function of Cortex.—From a long series of experiments [15] I found that the character of the cortical motor discharge was greatly altered, that is, soon exhausted, and without after-effects, and diminished until in the cretinous condition when voluntary movements became exceedingly slow and imperfect, excitation of the cortex was without appreciable result. The same thing was true for excitation of the corona radiata and spinal cord.

The point was subsequently reinvestigated by Autokratow, who found that in the height of the spasms the excitability not only of the centres but also of the peripheral nervous system was notably increased (to both the faradic and constant current), and that this persisted for some time after the conclusion of an attack. These results were confirmed by Schultze and Schwartz. This experimental demonstration of the functional failure of the higher centres ("middle level" of Jackson) is rendered complete by the clinical observation of loss of power in the highest, that is intellectual, centres, for thyroidectomy in animals produces the most exact repetition of the slowness of thought, the irritability, stupidity, and ultimately complete hebetude of the myxœdemic and cretinous human being. The one element in common is the loss of the thyroid gland.

It is thus perfectly clear that the general toxæmic state caused by loss of the thyroid gives rise to excitatory and subsequently paralytic changes in the central nervous system. It does not follow that the alteration in the blood itself is the only change required, on the contrary doubtless the connective tissues of the nerve centres undergo the same degenerative changes as the other parts of the body and the nerve protoplasm proper, that is, of the corpuscles and fibres suffers in consequence.

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[15] *Report to the Clinical Society.*

Symptoms of Disorder of the Blood.

Changes in Respiration.—The next most obvious set of changes are those due to the toxæmia itself. Most of these I have already referred to under the question of hæmapoiesis, but in connection with what has just been said concerning the neuroses exhibited there come up for consideration the remarkable changes in respiration. It has already been stated that the respiratory gas exchange in the blood is greatly altered, and the proper degree of oxygenation greatly reduced. The much increased rate of respiration noted in the carnivora by Schiff and all observers obviously may be due to this asphyxial[16] state of the respiratory centre. That it is so in part is shown by the observations of Schiff on the influence of artificial respiration in improving this state of affairs. But it is not the complete explanation. The accelerated respiration may be observed in spite of reoxygenation; in man indeed tracheotomy has been practised to relieve the dyspnœa in some cases of thyroid disease without result, although all mechanical obstruction was removed (Bruns), while Drobnick has found by direct inspection that the glottis was wide open during the most pronounced dyspnœa, and he concluded therefrom that there must be spasm of the bronchioles.

Further, the old view of Kocher, Lombard, and others that cachexia strumipriva and myxœdema are due to chronic asphyxia calls for remark in this connection, but may be dismissed at once, since König has shown that even repeated tracheotomy has no effect in arresting the cachexia, and it does not diminish the venosity of the blood (Albertoni and Tizzoni).

It is evident from all these facts that, as shown by Schnitzler and Seitz, there is another element at work. That element I believe to be changes in the functional ability and activity of the respiratory centre itself, due to the general lowering of metabolism as well as to the direct toxic influence of the altered blood. Proof of this bulbar failure is evidenced by other symptoms, that is, cardiac disturbance, difficulty of swallowing, and vomiting, while the well-known sensitiveness of the respiratory centre to external impressions is obviously the reason why it is the first to become disorganised. The further changes in the chemistry of the blood await research, and would greatly reward investigation.

Symptoms of General Derangement of Nutrition.

This group of symptoms is almost the most important, for, if carefully investigated, they would doubtless reveal the chemico-biological changes in the tissues which are disorganised by the loss of the thyroid's metabolic influence. So far as the gas exchanges of the blood are concerned, I have already alluded to the little that has so far been ascertained, but of course the effects and relation of such alterations to the vital activity of the tissues are quite unknown.

Tissue Changes.—In experimental thyroidectomy most observers have noted as the first prominent general change emaciation in the acute form. In man and monkeys the changes in the connective tissues are most interesting. Thus, in the early well-marked myxœdematous condition Halliburton

[16] Arguing from a slender basis of clinical fact, Grötzner believed that there was a definite relation between the pulmonary function and that of the thyroid gland.

has shown that in these animals there was an increase of mucin, and this has also been found, clinically, in a man by Charles for Ord. In one of my sheep this was extremely marked, both on chemical analysis and on microscopical examination.[17]

If, on the contrary, the cretinic state, as shown by my second series of experiments, supervenes, then no increase of mucin can be found, but instead, fibroid changes are noted, coupled with emaciation. This is true for man as well as monkeys.[18] Professor Virchow critically examined in the former the extraordinary œdema which is such a characteristic feature of the myxœdema stage, and suggests that it is a metaplasia of the subcutaneous fat into more mucous tissue, and this not with any diminution of volume, but an increase. The fact that when the disease is most acute the proportionate existence of mucin in the tissue is increased he considers to be due to some active, irritative, previous change rather than a kind of retention which apparently my publications seemed to convey. This latter idea, however, I have never held, my view being, as I stated in 1884, that the thyroid gland possesses a power of metabolising certain intermediate waste products, and that if this metabolism should be interfered with, the consequence was disorganisation of the chemical changes (more especially those of the connective tissues), resulting in the imperfect development and performance of their normal processes, and consequently in their exhibiting this form of mucinoid degeneration. As regards cretinism, Professor Virchow reminds us of the two forms, first, as we should now say, the myxœdematous form, and, secondly, the atrophic form, pointing out that, in theformer case, the resemblance between the so-called congenital variety of the disease and that developed in adult life is so marked as to lead us to believe they are quite identical in origin.

Occasionally the emaciation is not very marked, and is proportional to the acuteness of the cachexia. Clinically, in man, the most obvious change of nutrition is that of the skin. The skin becomes tough, coarse, and dry, from absence of secretion, the subcutaneous tissue thickened and inelastic, the hair falls out and becomes thin and grey, and profound alterations in the appearance are established. The same is observable in monkeys, though to a less degree, according as the skin is concealed or not by the hair. Conjunctivitis has been seen by several (Fuhr, Sanguirico with Canalis, Albertoni and Tizzoni, Ewald?) and is possibly due to the bulbar paresis referred to above. The chemical changes in the tissues, though disorganised, do not appear to lead to the excretion of any toxic substances in the kidneys, since Alonzo has found that in the carnivora subcutaneous injection of the urine secreted during the height of the cachexia produces no more effect than that produced by the kidneys under ordinary circumstances.

This group of symptoms thus indicates a grave disturbance of the basis of nutrition, namely, the active change of material in the tissues. What is most needed at the present time is the analysis of these changes compared with those observed in the blood.

The Disorder of the Heat Changes.—We will next glance at a

[17] *Vide* drawing in Report to the Clinical Society.
[18] Grundler, myself, Bourneville and Bricon.

most important symptom, which, though doubtless intimately connected with those just described, nevertheless deserves special consideration. Most noteworthy in the description of the phenomena following loss of the thyroid gland is the question of heat exchange. Briefly, the case may be considered (*a*) so far as intrinsic changes are concerned; (*b*) so far as extrinsic changes have to be dealt with.

(*a*) By intrinsic changes I mean the modifications which are introduced into the normal heat balance of the individual subject of experiment after elimination of any traumatic pyrexia due to the wound. These may be further subdivided as "early" and "late." Early changes in the temperature of the body are those which accompany the onset of the spasms and tetany. Thus during the acme of the muscular twitchings the temperature has been observed (Herzen, Ughetti, Alonzo, Rogowitsch, myself) to rise to 4° or 5° above the normal (to 43.4° C. in the dog, Herzen). The coincidence of this pyrexia with the general nerve disturbance suggests that the rise of temperature is dependent as much upon derangements of the heat-controlling centres of the nervous system as due to the chemical changes in the muscles, etc. After this commencing pyrexia the temperature begins to fall steadily until for days before death it is subnormal, sometimes even falling 4° C. or in monkeys to 92° F. (Schiff, Horsley, Sanguirico with Canalis, Ughetti, Alonzo, Rogowitsch, Herzen). It is thus clear that the fall of metabolism is indicated, not merely by degenerative changes in the tissues, but also by this remarkable fall in the temperature. Exact confirmation of the same phenomenon is derived from clinical records, since in the myxœdematous state in man the subnormality of the temperature is one of the most constant features of the disease. This latter point introduces us to the effect of extrinsic changes.

(*b*) By extrinsic changes of temperature a remarkable and serious influence is exerted upon the cachexia, greatly exaggerating the symptoms when the outside temperature is lowered, and, on the contrary, producing amelioration when warmth is applied (myself). Munk states that no such effects are produced by temperature. The beneficial effect of heat and the depressant action of cold, however, is very well known to patients suffering from myxœdema, cachexia strumipriva, and cretinism, and heat plays a very important part in the treatment of these disease conditions. Doubtless the extrinsic action of a rise of temperature is owing to its importance in aiding the already hampered chemico-biological processes.

Conclusions.

Such summaries of the leading symptoms in the cachexia as the space at my disposal enables me to give I have now made. I desire only to point out that the differences in the various classes of animals and in individuals of the same class when investigated will infallibly be found to demonstrate the universal application of the results of experiment, and that, like all complex and far-reaching processes, the cachexia is a compound of several factors. Under these circumstances it will vary in phases according to the special predominance of one or other factor. I would venture, therefore, to repeat here the classification of the symptoms which I published elsewhere as follows:—Stage I. Neurotic. Stage

II. Myxœdematous. Stage III. Cretinic. According to the virulence of the cachexia death may occur in any of these stages, but given any case of total disease of the thyroid gland the symptoms of the cachexia will invariably be found to follow the order just given, and any set of symptoms can be selected and referred to their proper position in the evolution[19] of the cachexia in each particular individual.

Summing up the foregoing pages, it seems to me that the thoughts and method of reasoning of Hofrichter on this subject have not been sufficiently before the minds of those who have taken up the question of the function of the thyroid. Hofrichter early in this century objected to the anatomical theories which regarded the gland as a mere diverticulum of the cerebral circulation, and his objection was logically founded on the simple fact that no experimental proof of such theories existed. From thence he proceeded to discuss the relations of the gland, and by the procedure of exclusion arrived at the definite opinion that it acted on the blood, deoxydising it, and in other ways chemically changing it. The same line of thought was pursued by Vest, who argued that the thyroid altered the blood, but he was led to believe that this alteration increased the assimilation of the chyle, for the support of which belief of course no facts are available.

The broad views expressed in the writings of these early writers find confirmation in every fresh investigation of modern research, for, with the mass of facts now at our disposal, it can be scarcely gainsaid that in the first place the thyroid gland does play a definite part in the economy, and that the cachexia which follows its removal is not due, as has been alleged, to injuries of the nerves in the neck.

Further, the more careful examination of the structure of the gland has shown that it is a secreting structure, and consequently operates by influencing the metabolism of the blood and therefore of the other tissues.

The behaviour of the tissue in responding by hypertrophy, when a part of the gland is lost, the fact that a certain proportion must be maintained for the purpose of health, that its (metabolic) importance varies directly with the activity of the vital processes, and is consequently greater in early life and diminishes with age—all demonstrates indirectly the worth of the gland and in fact its indispensability.

Crucial evidence upon these latter points is afforded by the remarkable results of transplantation of thyroid tissue in animals.

Finally, the array of symptoms evoked by extirpation of the gland, the constancy of their appearance and the remarkable differences exhibited in the rapidity and extent of their development according to the special metabolism of the class of animal under observation establishes clearly the position which the gland occupies in the economy of the body.

So definite and pronounced is the cachexia thyroidectomica that few subjects in the range of pathology offer a more fruitful and inviting field of research. That others may be tempted to enter upon it and extend our knowledge of this matter is the object of these remarks.

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[19] An interesting confirmation of my views as to the sequence of events evoked by loss of the thyroid is afforded by a case in which the true symptoms of myxœdema were preceded by tetany, and which is reported by Stewart, who, however, refers the condition to a hypothetical lesion of the sympathetic.

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